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Scaling of a filtration process

NOTE
Product names and filter sheet grades may have changed since the application note was created.

Author: Bettina Ledergerber

FILTROX AG, Moosmühlestrasse 6, 9001 St.Gallen, Switzerland
E-mail: applications@filtrox.com

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Content

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Abstract

In the context of process development in the pharmaceutical, biotechnological, or chemical industry, an increase in scale of the individual process steps is to be implemented, a so-called scale-up or also upscaling. Here, different key figures are decisive, depending on the respective process step. For the scale-up of the depth filtration step, for example, the required filter area is crucial. If precoat filtration is carried out using depth filters, the cake volume must also be considered, which is usually the limiting factor. In this application note, the scale-up of a yeast cell suspension is shown. Due to the rather low yeast cell count, a standard depth filtration was performed without the addition of a filter aid and thus without building up a filter cake.

1 Introduction

The correct scaling of different process steps is essential to minimize eventual risks in the subsequent scales. Therefore, the filtration step of a yeast suspension will also be scaled up to 20 L. As shown in figure 1 below, the first laboratory scale filtration tests were performed using the FILTROSPIN™ 20. The main purpose of this step is to evaluate the turbidity reduction provided by different filter sheet types. Once the filter sheet is determined for the corresponding product to be filtered, further tests can be carried out with the next larger filter system. The scaling factor [SF] is calculated based on the filter area.

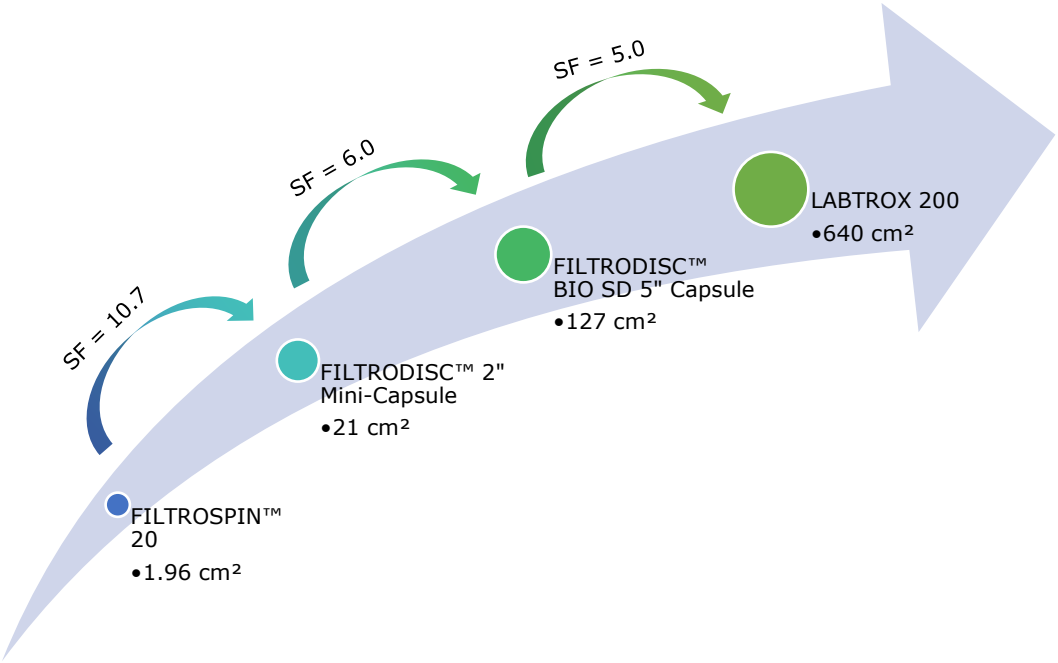

Figure 1: Scale enlargement overview of the filtration step of a yeast cell suspension. The indicated scaling factors [SF] refer in each case to the filter areas of the individual systems.

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2 Scale-up Step 1

All materials used in the first filtration step are listed below. FILTROSPIN™ 20 with different filter sheet inserts were used, each with a filter area of 0.000196 m². The pre-rinsing, the description of the method and the results obtained are also described in this chapter.

2.1 Material

The test system consisted of a centrifuge (Universal Centrifuge Z 287 A from Hermle Labortechnik GmbH), FILTROSPIN™ 20 spinner with different incorporated PURAFIX® depth filter sheets (FILTROX), and centrifuge tubes (LABCON® SuperClear®). The Eutech TN-100 turbidimeter (Thermo Scientific™) was used to measure the turbidity.

2.2 Rinsing

In order to flush all loose particles out of the depth filter sheet, it is usually recommended to flush the sheets with 50 L/m² of water or another process-compatible solution before each filtration test. For the FILTROSPIN™ 20, this would correspond to a rinse volume of 9.8 mL. Since filtration is possible without the previous rinsing step, this step was omitted. The filtration performance is comparable to filtration including the previous rinsing step.

2.3 Methods and Results

Six different FILTROSPIN™ 20 types were selected for the first process step. In each case, 20 mL of the cell suspension was added to each FILTROSPIN™ 20 and subsequently centrifuged at 3000 g. An overview of the filtration tests is shown in table 1 below. In each case, a six-fold determination of the turbidity measurement was performed, the mean values are given here. Since filtration takes longer for filter sheets with finer porosity (such as PURAFIX® CH ST 130P as well as CH ST 145ZP), the centrifugation time for these sheets was increased from 2 to 6 minutes. Figure 2 shows the average turbidity values graphically. The turbidity after filtration with the PURAFIX® CH 9P had a similar value to that of the unfiltered cell suspension. This indicates that the cells were forced through the filter sheet inside the respective FILTROSPIN™ 20.

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Table 1: Overview of the filtration tests performed on a laboratory scale with FILTROSPIN™ 20. 20 mL of the cell suspension was added to each FILTROSPIN™ 20 spinner and centrifuged for the specified time. For finer filter sheets such as the CH ST 130P as well as the CH ST 145ZP, the centrifugation time had to be increased due to the finer retention rate.

Test no.	Filter sheet	Centrifugation time	Turbidity*
Unfiltered solution	N/A	N/A	1'726.54 ± 13.37 NTU
1.1	FILTROSPIN™ 20 CH 9P	2 min	1'730.94 ± 1.85 NTU
1.2	FILTROSPIN™ 20 CH 31HP	2 min	214.78 ± 2.45 NTU
1.3	FILTROSPIN™ 20 CH 71HP	2 min	14.74 ± 0.70 NTU
1.4	FILTROSPIN™ 20 CH 101HP	2 min	6.17 ± 0.52 NTU
1.5	FILTROSPIN™ 20 CH ST 130P	6 min	3.02 ± 0.24 NTU
1.6	FILTROSPIN™ 20 CH ST 145ZP	6 min	2.46 ± 0.16 NTU

* Mean value, n = 6

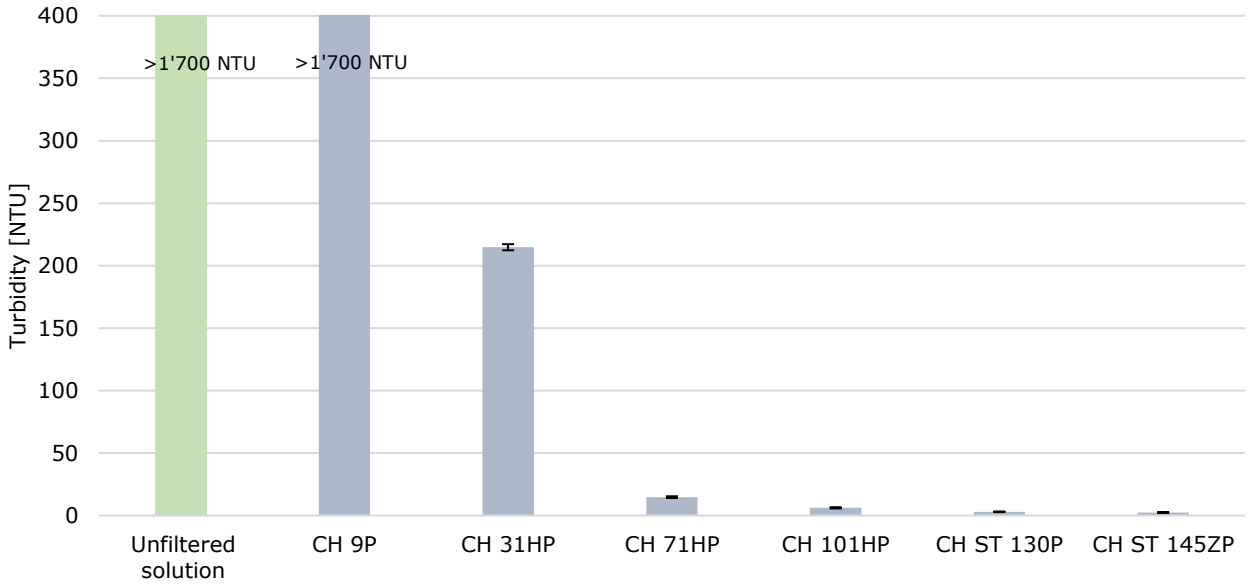

Figure 2: Turbidity values of the unfiltered suspension compared to the generated filtrates. Due to the high turbidity values of the unfiltered solution and the filtrate generated with the CH 9P filter sheet, the graphic was adjusted and the graphic bar is not shown completely.

A significant difference in turbidity reduction between the PURAFIX® CH 31HP, the CH 71HP, and the finer filter sheets CH 101HP, CH ST 130P and CH ST 145ZP can be seen. Based on these findings and based on the desired target values, it can be concluded that a PURAFIX® CH 71HP, CH 101HP or CH ST 130P would be best suited for this product.

Figure 3 below shows the generated filtrates after filtration with the FILTROSPIN™ 20 CH 9P, CH 101HP and CH ST 145ZP and compares each with the unfiltered yeast suspension. Figure 4 shows the filter surface of the CH 101HP after filtration as well as the cross-section of the filter sheet within the FILTROSPIN™ 20. Since the yeast suspension contained only a few cells, a standard depth filtration could be carried out without adding filter aids and thus performing alluvial filtration.

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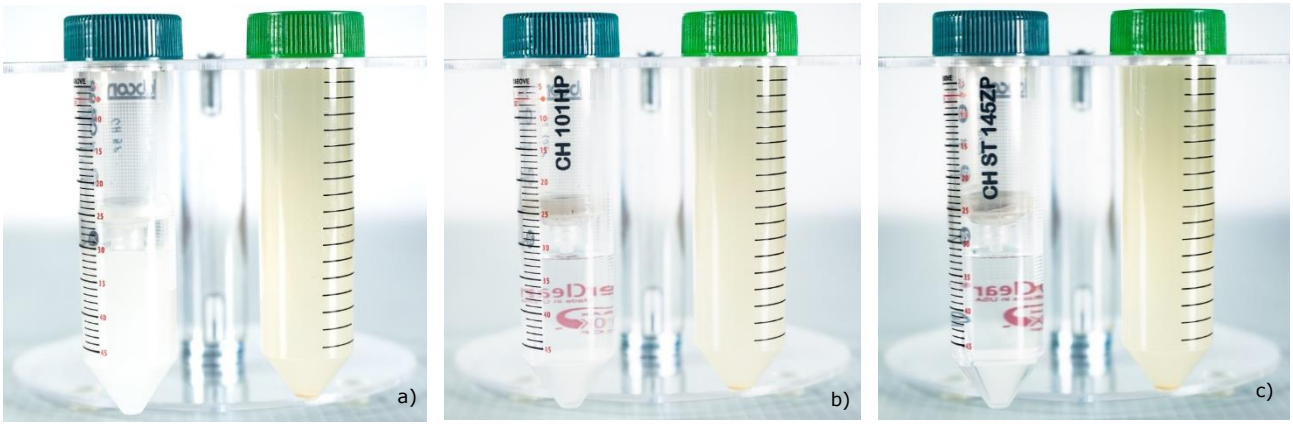

Figure 3: FILTROSPIN™ 20 CH 9P (a), CH 101HP (b) and CH ST 145ZP (c) each compared with the unfiltered yeast cell suspension. Since yeast cells were forced through the depth filter sheet PURAFIX® CH 9P during centrifugation, the filtrate produced accordingly is turbid. This was not the case with the other two filter sheets shown here.

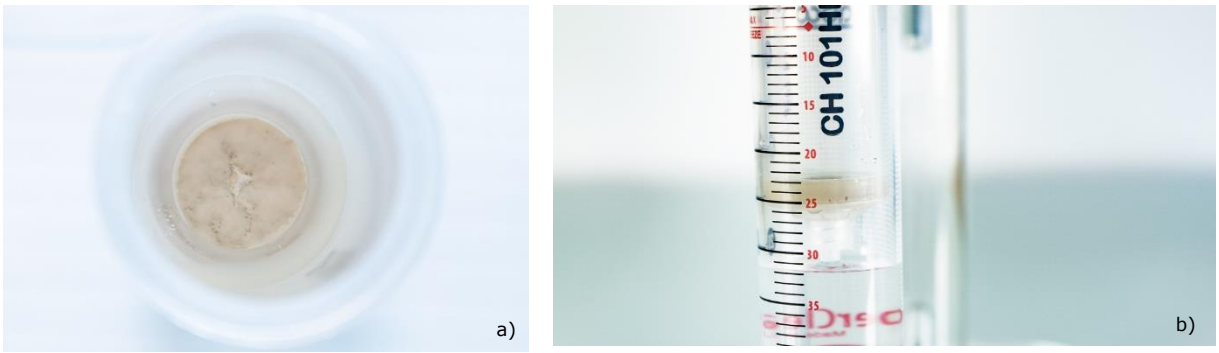

Figure 4: Filter surface (a) and the filter sheet inside the FILTROSPIN™ 20 CH 101HP (b). The yeast cells were retained on the surface of the PURAFIX® CH 101HP. Since only a few yeast cells were present, standard depth filtration could be performed.

3 Scale-up Step 2

FILTRODISC™ 2" Mini Capsule

For the second scale-up step, the FILTRODISC™ 2" Mini Capsule was used, in which a PURAFIX® filter sheet with a filter area of 0.0021 m² is inserted. Thus, a scale-up factor of 10.7 is achieved. All materials used, the methods and the results obtained are described below.

3.1 Material

The setup is shown in figure 5. The corresponding FILTROX PURAFIX® depth filter sheet was inserted into a FILTRODISC™ 2" Mini Capsule (FILTROX) (figure 5b). Subsequently, the capsule with the filter sheet was clamped into the synthetic filter holder (FILTROX) and this was attached to a laboratory stand (figure 5c). The inlet of the capsule was connected to a pressure gauge (TRI-MATRIX AG) via a #17 silicone hose (Shenchen Precision Pump Co. Ltd.). A peristaltic pump (Baoding Shenchen Precision Pump Co. Ltd. with the YZ1515x pump head) was used to deliver the yeast suspension. The maximum differential pressure of 2.5 bar should not be exceeded. Since the peristaltic pump used cannot exceed a maximum pressure of 2 bar, the experiments were stopped prematurely in each case. The turbidity of all samples was again measured using the Eutech TN-100 turbidimeter (Thermo Scientific™).

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Figure 5: Overview of the experimental setup and the individual parts of the filter capsule used. The experimental setup (a) consisted of a peristaltic pump, a pressure gauge and the filter capsule. Any filter sheet is placed between the individual parts of the Mini Capsule (b) and then sealed with the synthetic holder (c). Since yeast cells settled rapidly, the unfiltered suspension was continuously mixed using a magnetic stirrer. The filtrate was collected in a graduated cylinder each time to determine the filtered volume over time.

3.2 Rinsing

During the tests with the FILTRODISC™ 2" Mini Capsule, each filter sheet used was pre-rinsed with 50 L/m² ultrapure water before filtration. This means, a rinsing volume of 105 mL for the FILTRODISC™ 2" Mini Capsule with a filter area of 0.0021 m².

3.3 Methods and Results

Based on the measured turbidity values in the first upscaling step, three different PURAFIX® filter sheet types were tested for the further filtration tests with the FILTRODISC™ 2" Mini Capsule. As can be seen in table 1, there is a significant difference in turbidity reduction between the PURAFIX® CH 31HP and the CH 71HP. The reason for this is that some yeast cells are pushed through the PURAFIX® CH 31HP during filtration, which are retained in the finer-pored PURAFIX® CH 71HP. However, due to the centrifugal force, few cells are pushed through here as well, resulting in turbidity values of around 15 NTU. If these turbidity values are again compared with those from tests 1.4, 1.5 and 1.6, an even greater turbidity reduction is achieved. Therefore, the filter sheets PURAFIX® CH 71HP, CH 101HP and CH ST 130P were used for the following filtration tests with the 2" Mini Capsule. An overview of all filtration tests with the FILTRODISC™ 2" Mini Capsule is given in table 2 below. The chronological sequence of filtration rates, differential pressures as well as turbidity values of all tests can also be seen in figures 6, 7 and 8.

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Table 2: Overview of the filtration tests with FILTRODISC™ 2" Mini Capsule. Only three of the six filter sheets tested were used again in these trials. Each filter sheet type was tested three times to obtain statistically relevant results. In each experiment, 600 - 700 mL could be filtered.

Test no.	Filter sheet	Volume Filtrate	Turbidity*
Unfiltered solution	N/A	N/A	1'726.54 ± 13.37 NTU
2.1		630 mL	0.21 ± 0.062 NTU
2.2	PURAFIX® CH 71HP	700 mL	0.23 ± 0.037 NTU
2.3		700 mL	0.28 ± 0.058 NTU
2.4		640 mL	0.18 ± 0.052 NTU
2.5	PURAFIX® CH 101HP	620 mL	0.18 ± 0.032 NTU
2.6		655 mL	0.23 ± 0.065 NTU
2.7		650 mL	0.27 ± 0.030 NTU
2.8	PURAFIX® CH ST 130P	650 mL	0.32 ± 0.022 NTU
2.9		610 mL	0.20 ± 0.022 NTU

* Mean value, n = 6

For all filtrations, regardless of the filter sheet used, a stable filtration rate of around 400 L/m²×h was achieved in each case. After about 35 to 40 minutes, the filtration rates decreased due to the increasing differential pressure. The measured turbidity values are all comparable and are below 0.4 NTU, which is significantly lower compared to the previous tests with the FILTROSPIN™ 20.

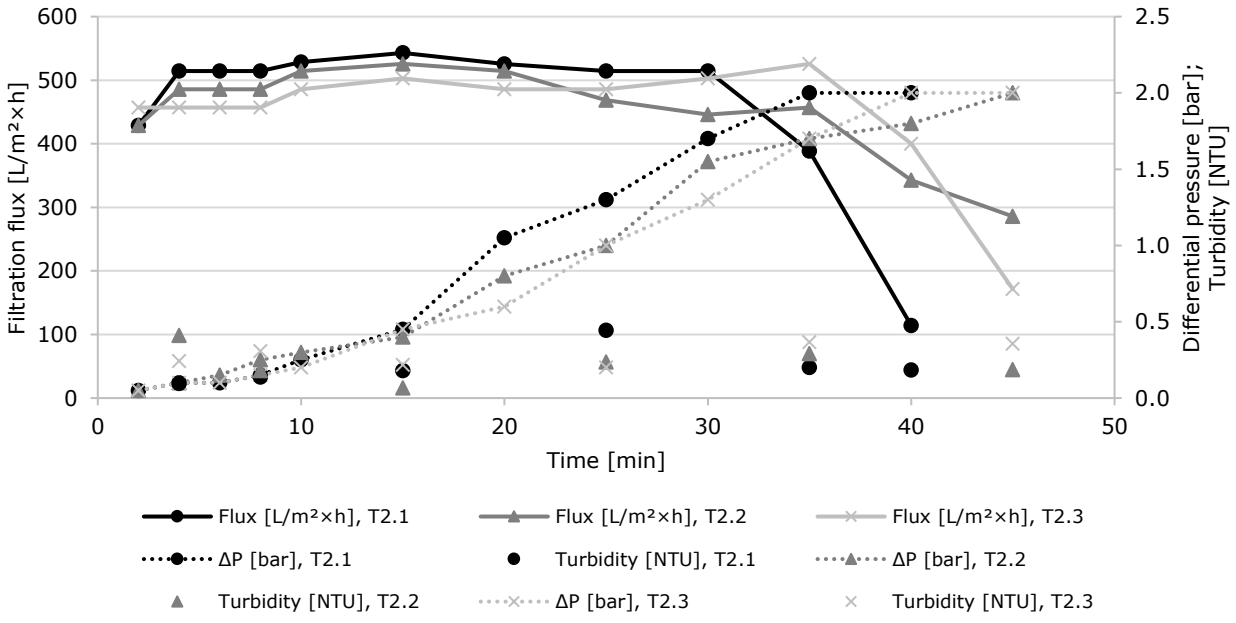

Figure 6: Filtration tests 2.1, 2.2 and 2.3 with the FILTRODISC™ 2" Mini Capsule. The chronological progression of filtration rate (flux), differential pressure and turbidity is shown. An initial turbidity of 1'726 NTU was measured.

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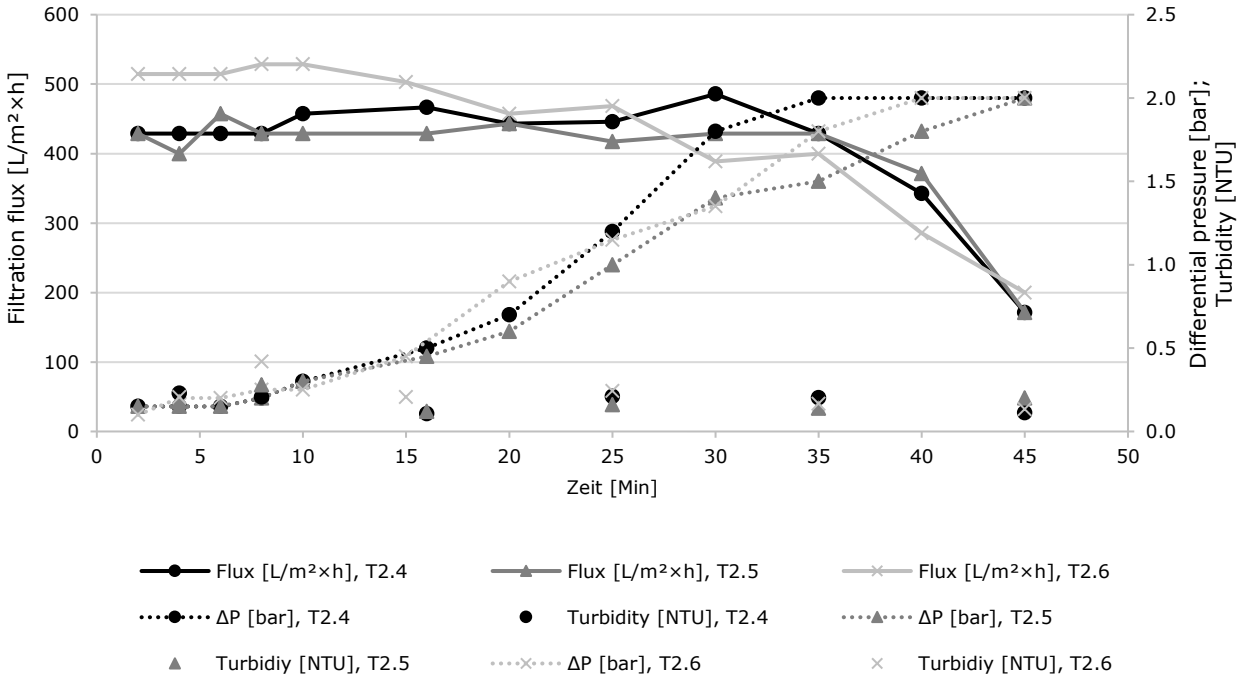

Figure 7: Filtration tests 2.4, 2.5 and 2.6 with the FILTRODISC™ 2" Mini Capsule. The chronological progression of filtration rate (flux), differential pressure and turbidity is shown. An initial turbidity of 1'726 NTU was measured.

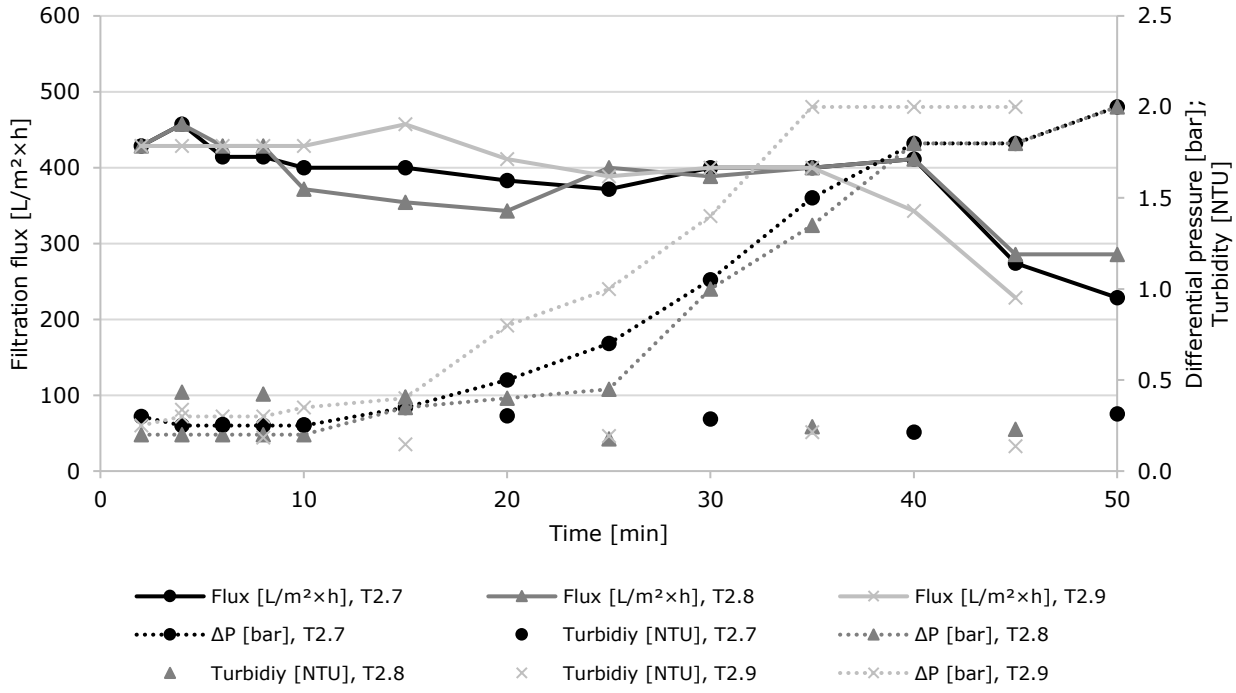

Figure 8: Filtration tests 2.7, 2.8 and 2.9 with the FILTRODISC™ 2" Mini Capsule. The chronological progression of filtration rate (flux), differential pressure and turbidity is shown. An initial turbidity of 1'726 NTU was measured.

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4 Scale-up Step 3

The third scale-up step was performed with the FILTRODISC™ BIO SD 5" filter capsule, which contains a filter sheet with a filter area of 0.0127 m².

4.1 Material

The setup for these filtration tests was identical to the setup with the FILTRODISC™ 2" Mini Capsule. The only difference is the filter capsule used.

4.2 Rinsing

As in the previous filtration tests with the FILTRODISC™ 2" Mini Capsule, each filter sheet inside the FILTRODISC™ BIO SD 5" filter Capsule was pre-rinsed with 50 L/m² ultrapure water before filtration. Due to the increased filter area, this corresponds to a rinsing volume of 635 mL.

4.3 Methods and Results

Based on the turbidity values obtained in the scale-up step 2, the PURAFIX® CH 101HP filter sheet was used in the third scale-up step only. Three identical filtration tests were performed (see table 3 for an overview of the three filtration tests).

Table 3: Overview of the filtration tests with the FILTRODISC™ BIO SD 5" Capsule. Due to the turbidity results of the previous upscaling steps, the filter sheet PURAFIX® CH 101HP was used only. To obtain statistically relevant results, a triplicate determination was performed.

Test no.	Filter sheet	Volume filtrate	Turbidity*
Unfiltered solution	N/A	N/A	1'726.54 ± 13.37 NTU
3.1	PURAFIX® CH 101HP	5.1 L	0.58 ± 0.046 NTU
3.2	PURAFIX® CH 101HP	5.6 L	0.30 ± 0.052 NTU
3.3	PURAFIX® CH 101HP	5.15 L	0.65 ± 0.036 NTU

* Mean value, n = 6

Figure 9 below shows the chronological progression of filtration rates, differential pressures, and turbidity values for the three tests. In all filtration experiments, a volume of more than 5 liters could have been filtered, with stable filtration rates between 370 and 400 L/m²×h. As with the filtration tests using the FILTRODISC™ 2" Mini Capsule, a decrease in filtration rates was noted after a certain point due to the increasing differential pressure. The turbidity values are minimally higher compared to the values from the previous tests, but they are all well below 1 NTU.

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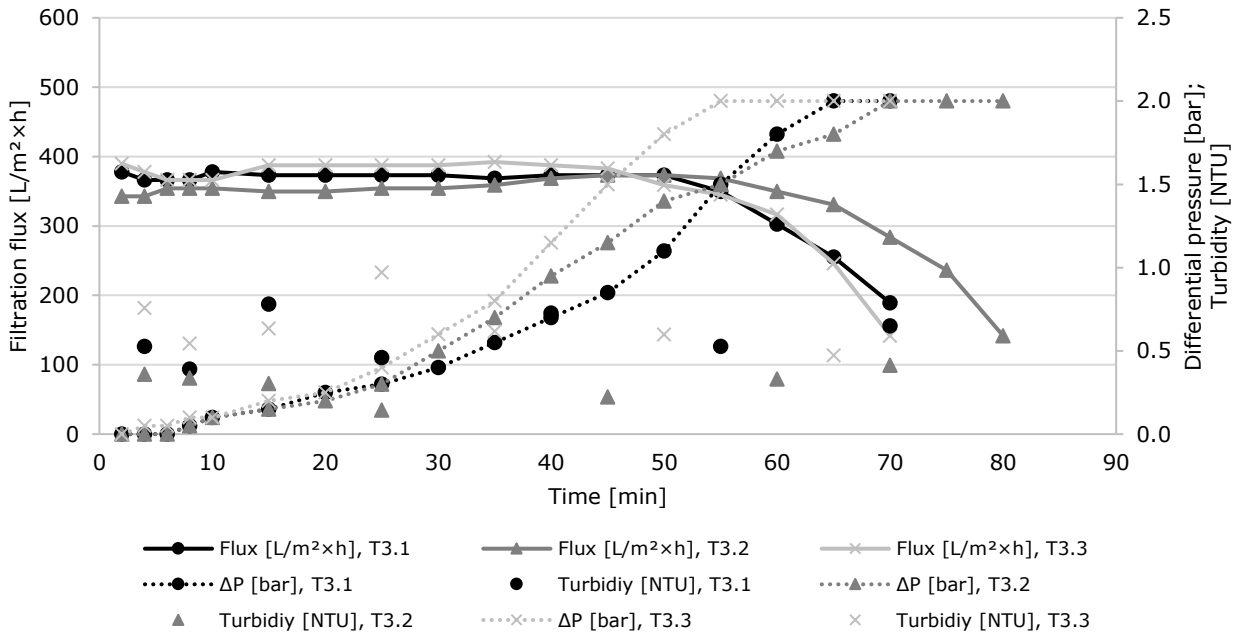

Figure 9: Filtration tests 3.1, 3.2 and 3.3 with the FILTRODISC™ BIO SD 5" Capsule. The chronological sequence of filtration rate (flux), differential pressure, and turbidity is shown. An initial turbidity of 1'726 NTU was measured.

5 Scale-up Step 4

The LABTROX 200 stainless steel housing was used for the fourth and final step. Two filter sheets in the format of 200 × 200 mm can be installed per filtration test, resulting in a total filter area of 0.064 m². Thus, a scaling factor of 5.0 is achieved (from the previous step with the FILTRODISC™ BIO SD 5" Capsule to the LABTROX 200).

5.1 Material

The filtration experiments were performed with a similar setup as shown in chapter 3 and 4, for the filtration experiments with the 2" Mini Capsule and the FILTRODISC™ BIO SD 5" Capsule, respectively. After inserting two PURAFIX® CH 101HP depth filter sheets, the unfiltered yeast cell suspension was pumped using the same peristaltic pump. Again, silicone tubing #17 (Shenchen Precision Pump Co. Ltd.) was used.

5.2 Rinsing

Before each of the three filtration tests, the filter sheets were pre-rinsed with 3.2 L ultrapure water. This corresponds to the recommended rinsing volume of 50 L/m² for the LABTROX 200 filter with a total filter area of 0.064 m².

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5.3 Methods and Results

As in scale-up step 3, three identical filtration tests were carried out, each with the PURAFIX® CH 101HP. An overview of the tests including the results (filtered volume as well as turbidity values) are shown in table 4 below. In addition, the chronological course of the filtration rate, the differential pressure and the turbidity values can be seen in figure 10.

Table 4: Overview of the filtration tests with the LABTROX 200 stainless steel housing. Again, three identical filtration tests were carried out, all performed with the PURAFIX® CH 101HP filter sheet.

Test no.	Filter sheet	Volume filtrate	Turbidity*
Unfiltrated solution	N/A	N/A	1'726.54 ± 13.37 NTU
4.1	PURAFIX® CH 101HP	21.5 L	0.48 ± 0.041 NTU
4.2	PURAFIX® CH 101HP	26.5 L	0.90 ± 0.061 NTU
4.3	PURAFIX® CH 101HP	24.0 L	0.55 ± 0.050 NTU

* Mean value, n = 7

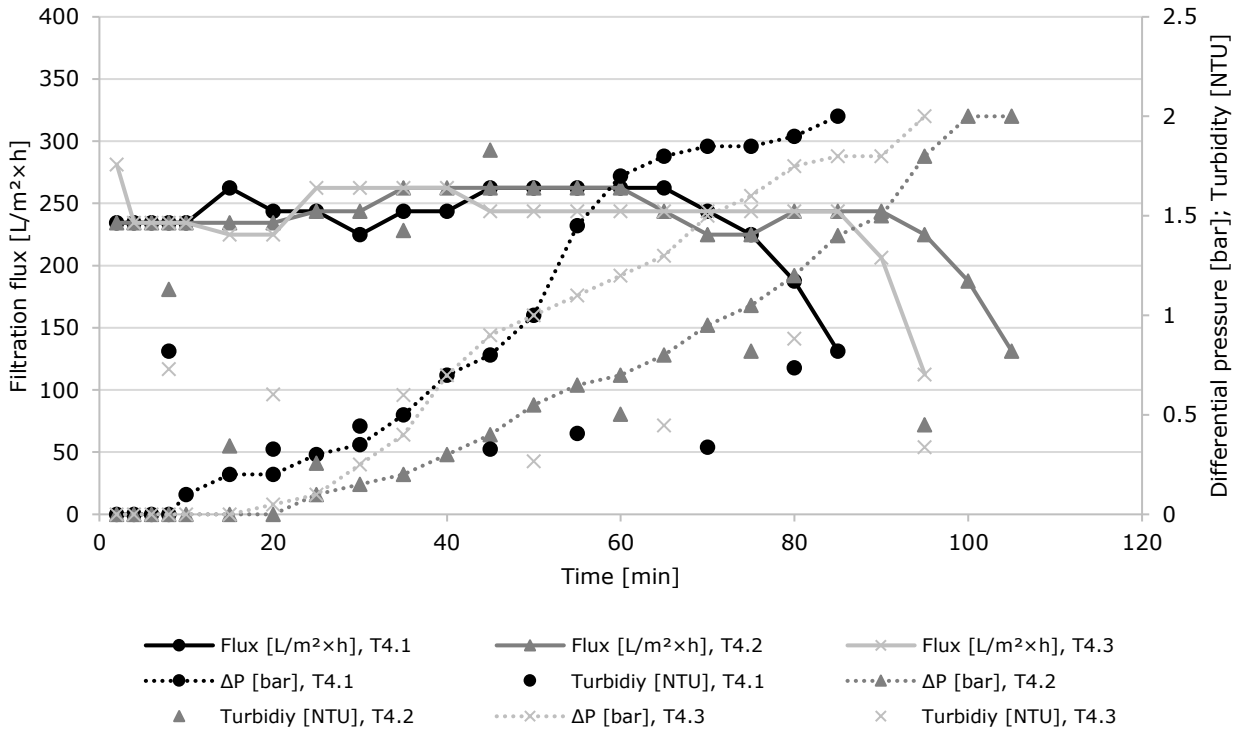

Figure 10: Filtration tests 4.1, 4.2 and 4.3 performed with the LABTROX 200. The chronological sequence of the filtration rate (flux), differential pressure and turbidity is shown. An initial turbidity of 1'726 NTU was measured.

Due to the limited rotational speed of the peristaltic pump, a filtration rate of only around 250 L/m²×h could be achieved. However, stable filtration rates were also measured here up to a certain point. Only after a stronger increase in the differential pressure did the filtration rates also drop.

6 Conclusions

Filtration tests on a laboratory scale are essential. This minimizes potential problems and risks in the subsequent pilot or production scale. The described filtration trials of the yeast cell suspension have shown that a linear scale-up of a depth filtration step is feasible.

The following calculation [1] is used to determine the minimum required filter area for an appropriate batch size, whether for laboratory, pilot, or production scale. Table 5 shows the calculated values. The goal was to achieve a scale factor of 5 in each case. However, these calculations are not meaningful between steps 1 and 2 because the filtered volume is limited to 20 mL for the FILTROSPIN™ 20 filtration tests.

$$A_{prod.}[m^2] = \frac{V_{prod.}[L] \times A_{test}[m^2]}{V_{test}[L]} \qquad [1]$$

$A_{prod.}[m^2]$	Minimum required filter area in production scale (or a given batch size)
$A_{test}[m^2]$	Filter area, which was used for the laboratory tests
$V_{prod.}[L]$	Production scale volume (batch size)
$V_{test}[L]$	Laboratory scale filtered volume

Table 5 shows the scale-up parameter and the expected parameter for the next scaling step. The scale-up parameter are based on the results obtained in the corresponding tests, in particular on the volume that could be filtered. Based on this and including the filter area, the filter capacity was calculated. As mentioned before, the calculation from step 1 to step 2 is only conditionally useful, since the FILTROSPIN™ 20 is limited with respect to the volume of the unfiltered suspension.

The expected parameters were calculated with a scaling factor of 5 and are based on theory. These serve to define the next scaling step, respectively the suitable filter system for the next scale-up step.

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Table 5: Overview of the scale-up parameters calculated for each scale-up step, based on the filtration tests with the PURAFIX® CH 101HP. The scale-up parameters and the expected parameters derived from them are shown for all steps. The filter capacity, the expected filtrate volume for the subsequent scale-up step and the derived filter area could not be calculated for step 1 with FILTROSPIN™ 20 since the volume of the unfiltered cell suspension is limited due to the small size of a FILTROSPIN™ 20.

		1	2	3	4
	System	**FILTROSPIN™ 20**	**FILTRODISC™ 2" Mini Capsule**	**FILTRODISC™ BIO SD 5"**	**LABTROX 200**
Scale-up Parameter *	Filter area [m²]	0.000196	0.0021	0.0127	0.064
	Filtered volume [L]	0.02 ± 0.00	0.64 ± 0.014	5.28 ± 0.225	24.0 ± 2.041
	Filter capacity [L/m²]	N/A	303.9 ± 6.827	416.0 ± 17.704	375.0 ± 31.894
Expected Parameter **	Volume filtrate [L]	N/A	3.2 ± 0.072	26.4 ± 1.124	120.0 ± 10.206
	Filter area [m²]	N/A	0.0105 ± 0.000	0.0635 ± 0.000	0.32 ± 0.000

* Parameter calculated for the corresponding scale-up step.

** Expected parameter for the next scale-up step. The calculations for this are based on a scaling factor of 5.

The scaling of the depth filtration step of a yeast cell suspension worked very well. Only 6 different FILTROX filter sheets were tested during these trials. This showed that the PURAFIX® CH 101HP is ideally suited for the filtration of the yeast suspension. However, other filter sheets, for example PURAFIX® CH ST 110P, which is between CH 101HP and CH ST 130P in terms of retention rate, could also be suitable. In order to verify this, further filtration tests on a laboratory scale would be recommended.