WHITE PAPER

THE UPSCALING OF LACTOSE CRYSTALLIZATION TOWARDS A FULL CONTINUOUS CRYSTAL PRODUCTION

Scaling lab-tested process to pilot-scale for production verification

Secoya

FLUIDIFY PHARMA

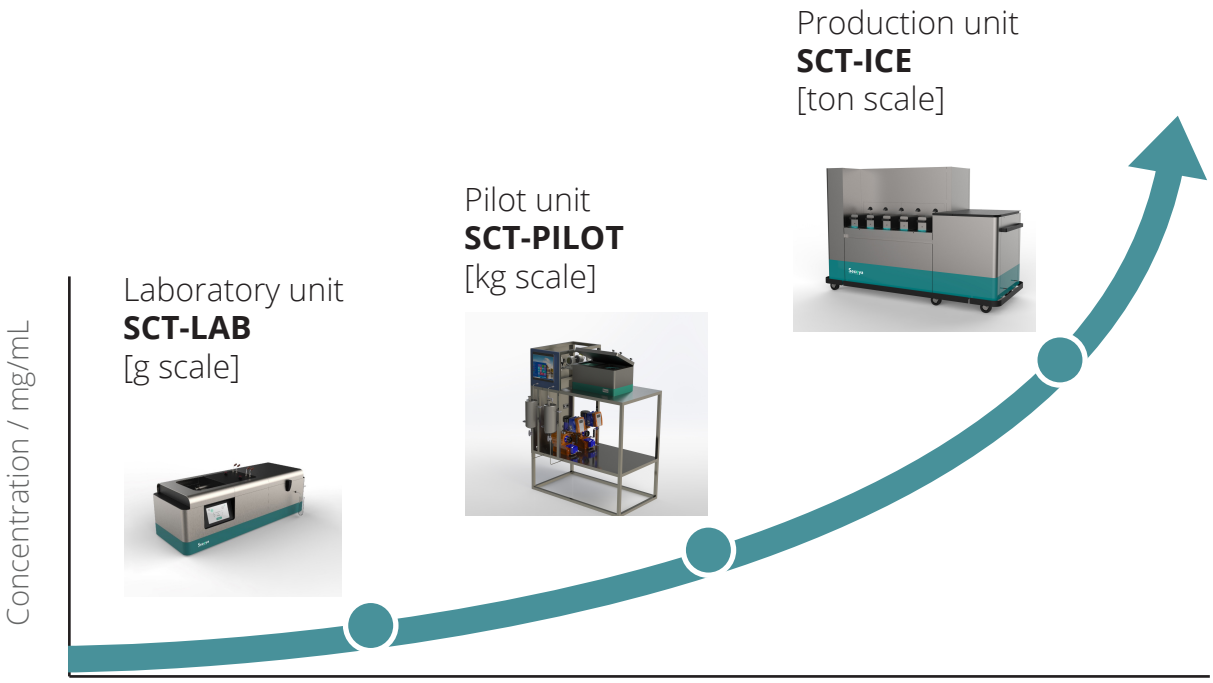

Figure 1: the upscaling route for crystallization processes using Secoya's instruments.

Introduction

Secoya Technologies is specialized in crystallization processes using their proprietary reactors and methodologies based on the spontaneous nucleation of solutes in solution flowing through capillary reactors. Thanks to its tight control of the number of nuclei produced per mL of solute, Secoya Crystallization Technology, or SCT, enables to drive the particle size of a crystallizing compound at its equilibrium state, prior to filtration.

To facilitate the study of the crystallization process itself, Secoya has developed a lab and a pilot instrument. The laboratory benchtop instrument is dedicated to the screening of parameters while using as little solute as possible.

The screened parameters are

- Solute concentration
- Solvent and antisolvent selection, the latter when required
- Type of mixing or agitation when required
- Solution temperature
- Nucleation temperature
- Flow rate(s)
- Residence time at temperature
- First indication of crystal growth duration after collection outside of the SCT reactor

Once these parameters have been set, the complete dataset is copy-pasted onto the pilot-scale unit. This unit allows batches of up to 2.5 l solution to be produced at once, using the identical combination of mixing (if required) and reactor as defined in the lab screening tests.

Compared to the laboratory unit, the pumping system is replaced by a full continuous pumping unit, maintaining the same flow rate quality as compared to the lab unit through to multiple parameters control like pump rate, back pressure and mass flow regulation.

This regulation is then in a later stage used for mass flow control through multiple parallel placed reactors in the final industrial scale (ICE).

The pilot unit is used to confirm that data obtained at the lab scale with pumping and fluid control system adapted to the scale of continuous industrial production unit (ICE). It also allows the production of the necessary volume of material for a complete powder characterization.

A full production calculation per reactor, crystal growth parameters, filtration strategy, and productivity extrapolation for a fully designed ICE unit are other important features that are investigated on this unit.

Lactose-based solubility study

Lactose was used as a model compound to demonstrate the capability of the Secoya Crystrallization Technology The set goals were to obtain a particle size distribution of the product in the range given in Table 1, using water as solvent and without the use of any antisolvent. The solubility of lactose in water is shown in Figure 2. Lactose has a large difference in solubility at low and high temperatures. A large supersaturation zone needs therefore to be covered upon screening of the crystallization conditions. A study by Hartel and Liang (J Dairy Sci, 1989) had previously demonstrated that lactose crystallization requires long induction times at already fairly high supersaturation rates up to sigma=2.8, with the supersaturation sigma given by

$$\text{sigma} = \frac{C_{solution} - C^*}{C^*}$$

Table 1: Particle size prerequisites for Lactose in this study

Particle attribute	Size / µm
D10	30
D50	60
D90	90

With $C_{solution}$ the investigated solution concentration and C^* the solubility value at the investigated nucleation temperature. For example, a value sigma of 2.8 at room temperature, which has a C^* of 200 mg/mL represents a $C_{solution}$ of 760 mg/mL. In other words, a heated solution of 760 mg/mL lactose in water may nucleate when cooled down to 20 °C.

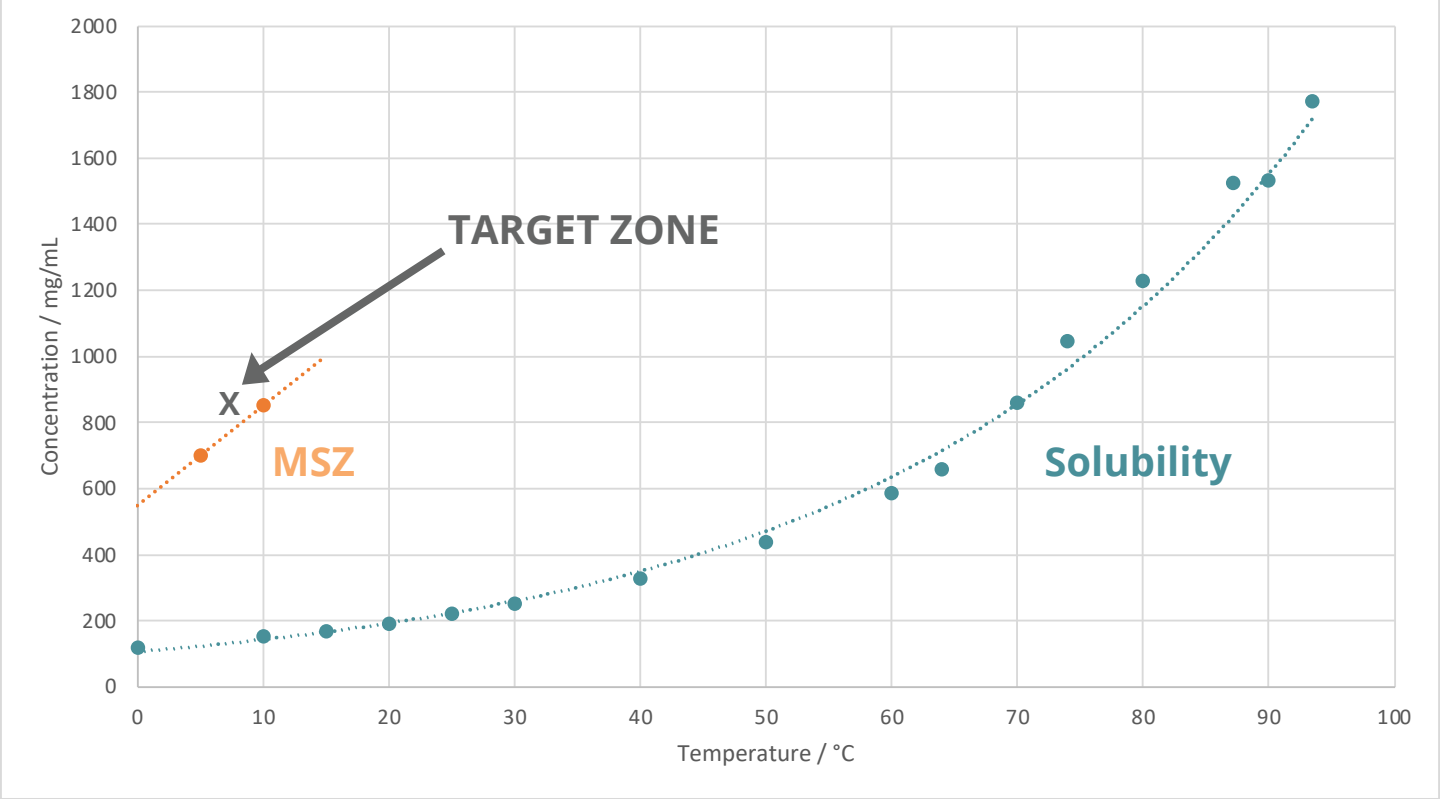

Figure 2: lactose solubility in water given in mg of solute per mL of solution as a function of temperature. In orange the experimentally foxed metastable zone (MSZ) and cross X the ideal combination retrieved for lactose at a concentration between 800 and 850 mg/mL and a nucleation temperature of 5°C.

Laboratory tests

As a first investigation, we always try to map the position of the metastable zone. This is performed using in this case two highly concentrated solutions given the previously discussed concentrations necessary for crystallization. A flow rate of 20 mL/min was applied for a fixed reactor volume of 7mL.

The solutions were prepared at 85°C and injected at that temperature into the SCT-LAB unit where they undergo a rapid cooling down to reach a target temperature in the phase diagram. As lactose crystals were described as slow growing crystals by the same authors, we then let the crystals equilibrate at 25°C and store the crystals. It was observed that a milky white slurry is created for the 700 mg/mL solution once threshold nucleation temperature of 5°C was crossed at sigma value 3.7.

The same happens for a 850 mg/mL solution at 10 °C, at identical sigma value. Microscopic images of this last sample are shown in Figure 3.

Large crystals are observed with a rather high dispersion between the crystals. However, we are able to draw the line for the initiation of nucleation inside our reactor when using the parameter set in Table 2: the orange dots in Figure 2 represent the crossing of the metastable zone observed inside our reactor. Please note that the other products showed after 24 hours some crystals, as nucleation may occur for these solutions at room temperature, but for which this nucleation did most probably not occur inside the tubular reactor given the high induction times.

Table 2: Metstable zone screening for lactose in water using 20 mL/min as flow rate for a 7 mL reactor. Solutions were prepared at 85 °C.

Fixed parameters		
Solution temperature	85°C	
Reactor	7 mL	
Premixing	Absent	
Flow rate	20 mL/min	
Sample storage	Room temperature	
Solution concentration / mg/mL	**Nucleation temperature / °C**	**Test result**
700	20	No crystals observed after 2 hours
700	15	No crystals observed after 2 hours
700	10	No crystals observed after 2 hours
700	5	Crystals observed after storage
700	0	Crystals observed after storage
850	20	No crystals observed after 2 hours
850	15	No crystals observed after 2 hours
850	10	Crystals observed after storage
850	5	Crystals observed after storage
850	0	Crystals observed after storage

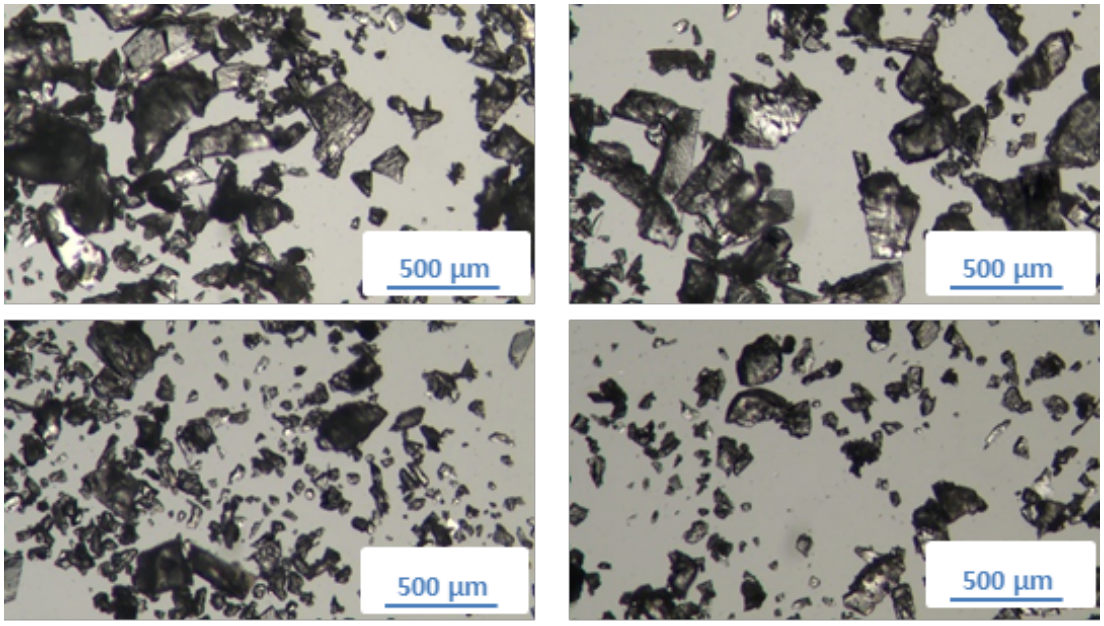

Figure 3: Lactose crystallization result using a starting concentration of 850 mg/mL and nucleation temperature of 5°C and conditions as set in Table 2.

Due to these results and further testing on this compound, a new specific reactor design was implemented at 7 mL total volume. A heated lactose solution of 850 mg/mL in water was injected at 20 mL/min flow rate in the reactor maintained at 5°C Further investigation also led to the decision to allow the crystals to grow at a temperature of 5°C during 180 minutes with agitation, in order to maximize the possible yield.

Several repeated tests were performed using these conditions to check on the repeatability of the performed tests at laboratory scale. Not only is the production of material constant – sample R1 might be considered as an outlier for average size – but the required particle sizes and distributions are reached, as is depicted in Figure 4: all values of D10, D50 and D90 lie inside the proposed limits as set out in Table 1.

Table 3: Optimal parameters set for the crystallization of lactose in water as well as the particle size analysis results obtained for 5 independent test runs on the laboratory unit. D10, D50, D90 represent the 10th, 50th and 90th percentile in size, respectively. Stdev is the standard deviation of the average particle size. 200 individual crystals were measured by taking the longest distance per crystal.

Process parameter	Current selection based on first tests
Insert	Specific execution
Reactor	Specific execution of a 7 mL reactor
Solution concentration	850 mg/mL
Solution starting temperature	85°C
Nucleation temperature	5°C
Flow rate	20 mL/min

Sample	average	stdev	D10	D50	D90
	µm	µm	µm	µm	µm
R1	57	19	35	53	83
R2	60	22	34	58	86
R3	65	21	41	63	93
R4	62	22	35	59	91
R5	65	23	39	63	97

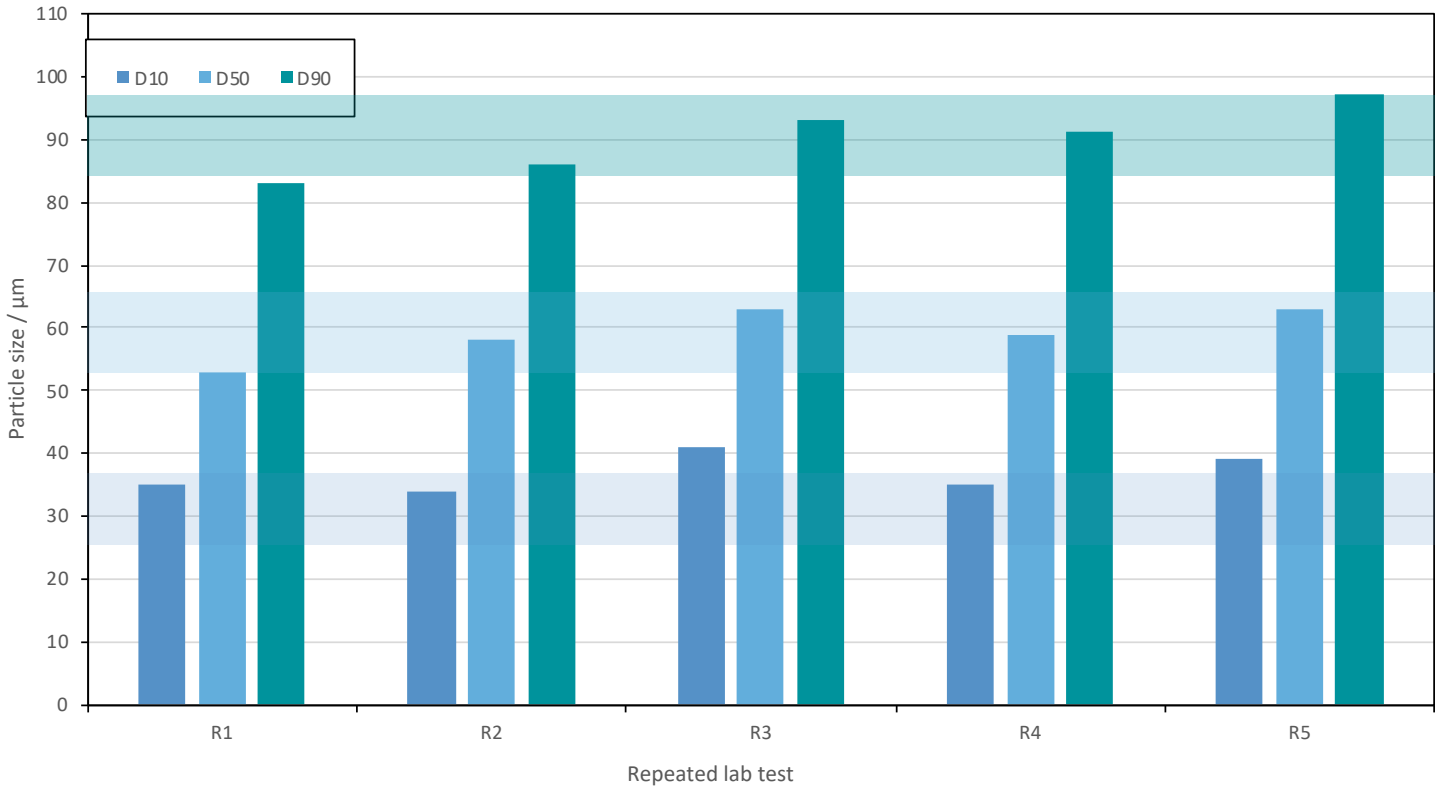

Figure 4: Particle size results of repeated lab tests using optimal conditions as set out in Table 3. Colored zones indicated required range for D10, D50 and D90 values.

Pilot tests

Once this was established, the same parameters set as proposed in Table 3 was used for screening on the SCT-PILOT unit. We used here 2 L of highly concentrated solution at 85°C. The complete solution is then injected into the specific 7 mL reactor.

Depending on the total flow rate, the total collection in the crystal growth tank might vary between 100 and 150 minutes. The crystalline material is then allow to grow during 18 hours at 5°C in order to ensure that the equilibrium state of the slurry is reached. This is validated using solids weighing after filtration and mother liquor analysis.

Among the parameters tests set shown in Table 4, the tests P1 and P2 highlighted in blue show identical parameters as the lab scaled test from Table 3. Both P1 and P2 show very comparable results as compared to the tests on laboratory scale. Indeed, when variability is plotted together with the repeated results at laboratory scale, very similar products are found, as shown in Figure 6.

Among the parameters test set shown in Table 4, the tests P1 and P2 highlighted in grey show identical parameters as the lab scaled test from Table 3.

Both P1 and P2 show very comparable results as compared to the tests on laboratory scale. Indeed, when variability is plotted together with the repeated results at laboratory scale, very similar products are found, as shown in Figure 6. Moreover, the results in Table 4 show that once the optimal set of conditions is varied while keeping a fixed concentration (P5 to P9), the particle size suddenly increases to values comparable to a batch crystallization test performed on the same volume, at 5°C – indicated in Table 4. This demonstrates that a variation in concentration as performed in P3 and P4, may lead to lower particle sizes as compared to P1 and P2. There, lowering the total flow rate helps to readjust the particle size to the wanted size ranges.

It should be noted that it is not possible to increase the flow rates further in this setup due to a maximum pressure setting of 15 bar, which coincides with the pressure drop inside the reactor.

All size measurements were performed using manual microscopic image analysis. Control tests with a laser diffraction instrument revealed that our D10 value is slightly overestimated, whereas both D50 and D90 values are nearly identical. This indicates that the required particle sizes of Table 1 are obtained on the pilot unit with the set of optimal conditions determined using the SCT-Lab.

Table 4: Parameter set tests performed on the pilot unit. Tests highlighted in grey show identical test setup as the optimal lab scale parameters set.

Sample	concentration	q solution	Tn	D10	D50	D90
	mg/mL	mL/min	°C	µm	µm	µm
P1	850	20	5	36	60	88
P2	850	20	5	49	66	85
P3	800	20	5	35	48	65
P4	800	17.5	5	44	67	100
P5	850	20	3	49	87	144
P6	850	20	6	65	91	124
P7	850	18	10	77	104	161
P8	850	18	5	66	91	105
test without reactor	850	20	5	66	91	111

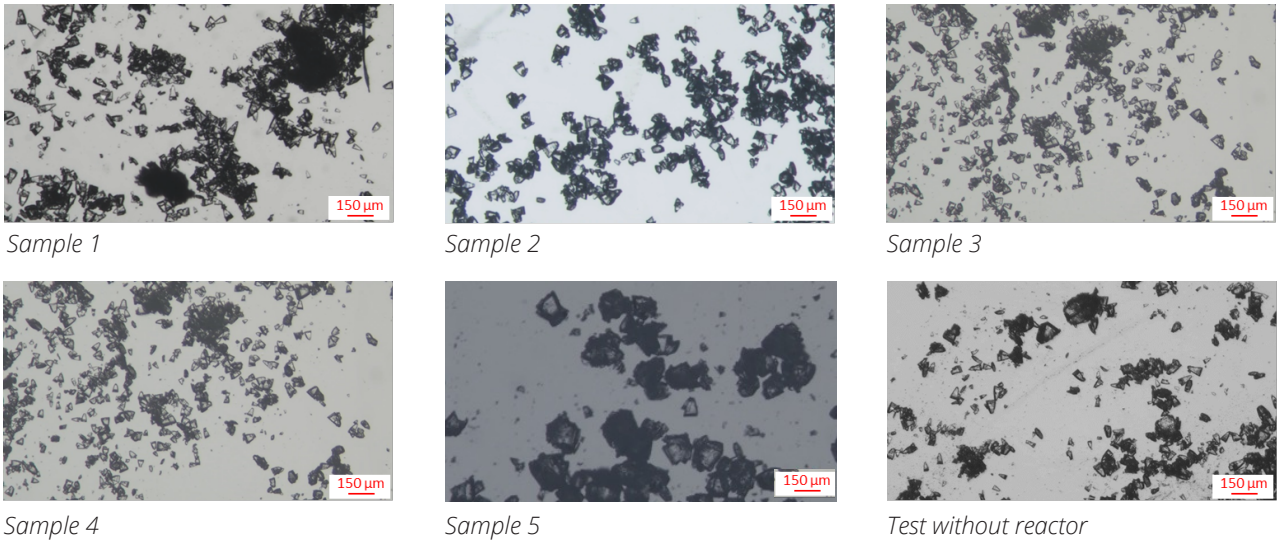

Figure 5: Microscopic images of crystalline samples after full growth and filtration for the tested conditions as set out in Table 4.

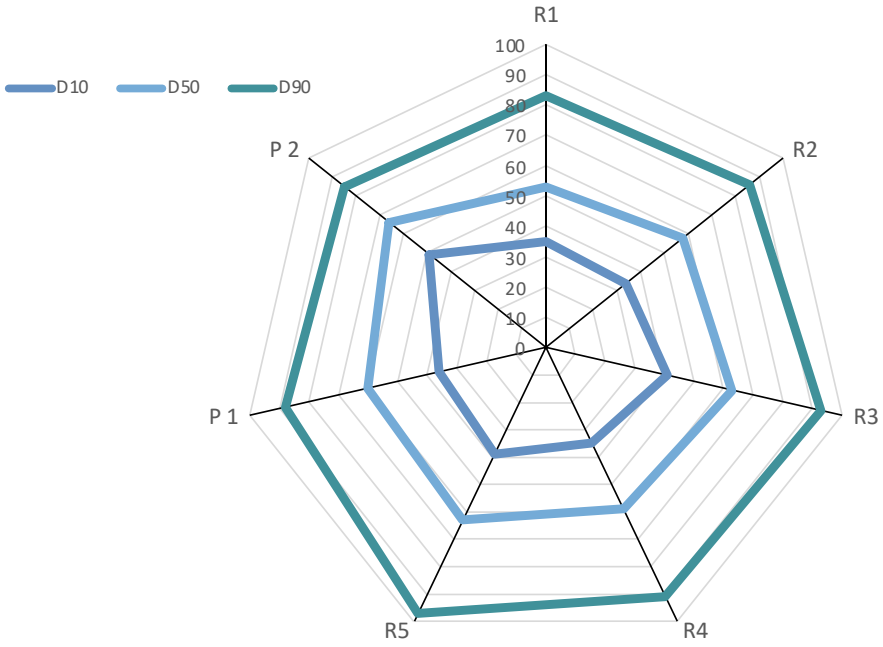

Figure 6: Lactose crystallization tests: extrapolation of results using identical parameters for both lab scaled testing (R1-R5) and pilot testing (P1 and P2). Parameter set as pointed out in Table 3 are used.

Yield and productivity

Filtration of slurry was carried out using a pressurized Nutsche filter equipped with a 3 µm polypropylene filter cloth. A pressure of 3 bar is sufficient to extract 100 mL slurry samples in 30 seconds. Depending on the solid content, filter cakes up to 45 mm were obtained.

In Figure 7 two of such retrieved cakes are shown. The highest cake is the one obtained after full crystal growth: the analyzed mother liquor showed a concentration of 150 mg/mL lactose which corresponds to the equilibrium state concentration C^* at 5°C.

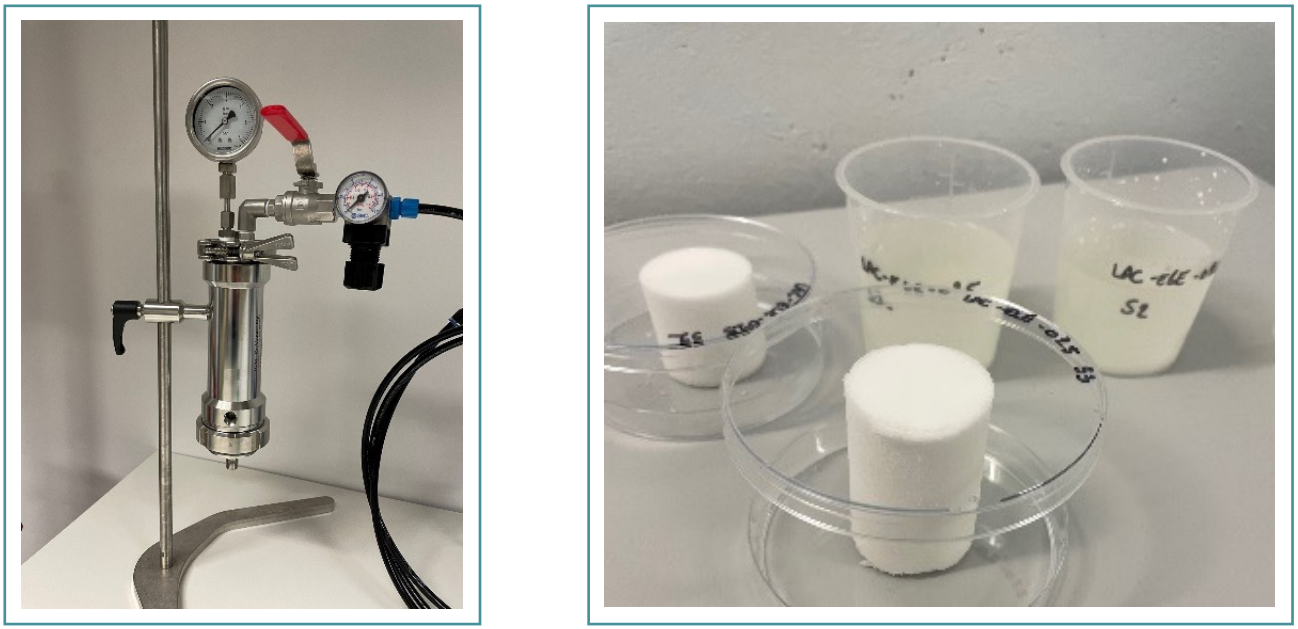

Figure 7: Nutsche filter cell (left) and two retrieved cakes after filtration, together with their respective mother liquor of test P5 taken after 12 hour and 18 hour of crystal growth at 5°C.

This residual 150 mL/mg concentration in the mother liquor means that from the initial solution concentration of 850 mg/mL, only 700 mg lactose per mL of water may crystallize. Weight measurements of dried cakes point out that we retrieve 90% of this material, which equals to 630 mg of solid lactose retrieved per mL of water. This represents 34% of the weight of the total initial solution. The density of the solution itself is measured as 1.15 kg/L solution. At a flow rate of 20 mL/min, 1.2 L or 1.38 kg of solution is injected inside each reactor per hour, with therefore an hourly production rate of dried lactose solid material per reactor of 470 g/h. In Table 5 some prognoses are made for the production of different batch sizes of lactose. Considering the aim of this project to produce on a weekly basis, a suited production rate should be attained, leaving sufficient time for a complete cleaning of the system on the basis of a 5 day working week. For example, a one ton production would take less than 43 hours to be treated inside the industrial ICE system with 50 reactors placed in parallel. In this example the total of 2560 L produced slurry would be injected into three separate tanks set at 5°C; once each tank is filled, the slurry is set for 18 hours at 5°C to let the crystals grow to the equilibrium state. Therefore, after at total time of 43 hours (tanks collection) + 18 hours (crystal growth), the batch production would be finished and the material ready for filtration, allowing sufficient time for a complete cleaning at the end of the working week.

Conclusions

Lactose was successfully crystallized using Secoya's Crystallization Technology. At the laboratory scale a suited parameters set was found to reach the desired particle sizes and distribution. This parameters set was successfully used at the pilot scale on kilogram scaled tests. Small variations in parameter settings had a drastic effect on the obtained particle size, which tended to increase towards size obtained in batch-based crystallization tests.

This demonstrated that a high control on the production parameters is primordial to have a constant output of the same quality of material. Small variations in initial solution concentrations, maintaining all other parameters constant, permitted to fine tune the particle sizes towards the target size.

A high yield of 90% combined with a flow rate of 20 mL/min resulted in a production of solids per reactor of 470 g/h. As the industrial scale units allows for a multitude of reactors to be placed in parallel, production batches up to 1000 kg of solids can be produced in a 5-day week, cleaning included.

About the author:

After completing his PhD at the Vrije Universiteit Brussel at the faculty of engineering on newly developed flame retardants, Bart Rimez worked for Benelux-Scientific, a vendor of analytical equipment for material characterization. Leaving this position, he led the "Flanders Microreactor and Microfluidics Consortium" or FMMC, where he was in contact with a vast network of technology innovators. in 2019, Bart co-founded Secoya-Technologies where he leads the crystallization process unit.

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