Supporting Information for

Continuous Flow Synthesis and Crystallization of Modafinil: A Novel Approach for Integrated Manufacturing

Diana V. Silva-Brenes,[a,b,¶] Shailesh Agrawal,[a,¶] Vilmalí López Mejías,[a,c] Jorge Duconge,[d] Cornelis Vlaar,[d] Jean-Christophe M. Monbaliu,[b,e] and Torsten Stelzer[a,d*]*

[a.] *Crystallization Design Institute, Molecular Sciences Research Center, University of Puerto Rico, San Juan, Puerto Rico 00926, United States*
[b.] *Center for Integrated Technology and Organic Synthesis, MolSys Research Unit, University of Liège, B-4000 Liège (Sart Tilman), Belgium*
[c.] *Department of Chemistry, University of Puerto Rico, Río Piedras Campus, San Juan, Puerto Rico 00931, United States*
[d.] *Department of Pharmaceutical Sciences, University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico 00936, United States*
[e.] *WEL Research Institute, Avenue Pasteur 6, B-1300 Wavre, Belgium*

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1. Continuous Setups for Flow Synthesis & Crystallization

1.1. Microfluidic Flow Synthesis Setups & Parts

All microfluidic setups were assembled with commercially available parts.

Reactors were built using High Purity PFA (perfluoroalkoxyalkane) tubing, with 1/16" outer diameter (OD), and 0.030" or 0.02" inner diameter (ID)

Pumps. Chemyx Fusion 6000 High Force syringe pumps equipped with stainless steel syringes (20 mL) and Fisher Scientific syringe pump 110V (Vendor Catalog # 780100I) were utilized to handle the liquid feeds.

Connectors, Ferrules, & Mixers. Capillaries were assembled with coned PEEK fittings or Super Flangeless PEEK nuts, ETFE ferrules and SS rings. Mixers consisted of PEEK T-mixers (0.02" through hole), PEEK cross- junctions (0.02" trough hole) or High Pressure mixing Tee UHMWPE Frit. Connectors, ferrules, unions and mixers were purchased from IDEX/Chrom Tech Inc. (details in Table S1).

Check-valves inserted between the pumps and the reactor were purchased from IDEX/ Chrom Tech Inc (PEEK check-valve holder).

Back-pressure Regulator (BPR). Dome-type BPR was purchased from Zaiput Flow Technologies (BPR-10). The dome-type BPR was connected to a compressed gas cylinder (nitrogen) to set the working pressure

Thermoregulatory Devices. PFA coils reactors were thermoregulated in oil baths with external thermocouples (VWR® Professional Hot Plate Stirrers).

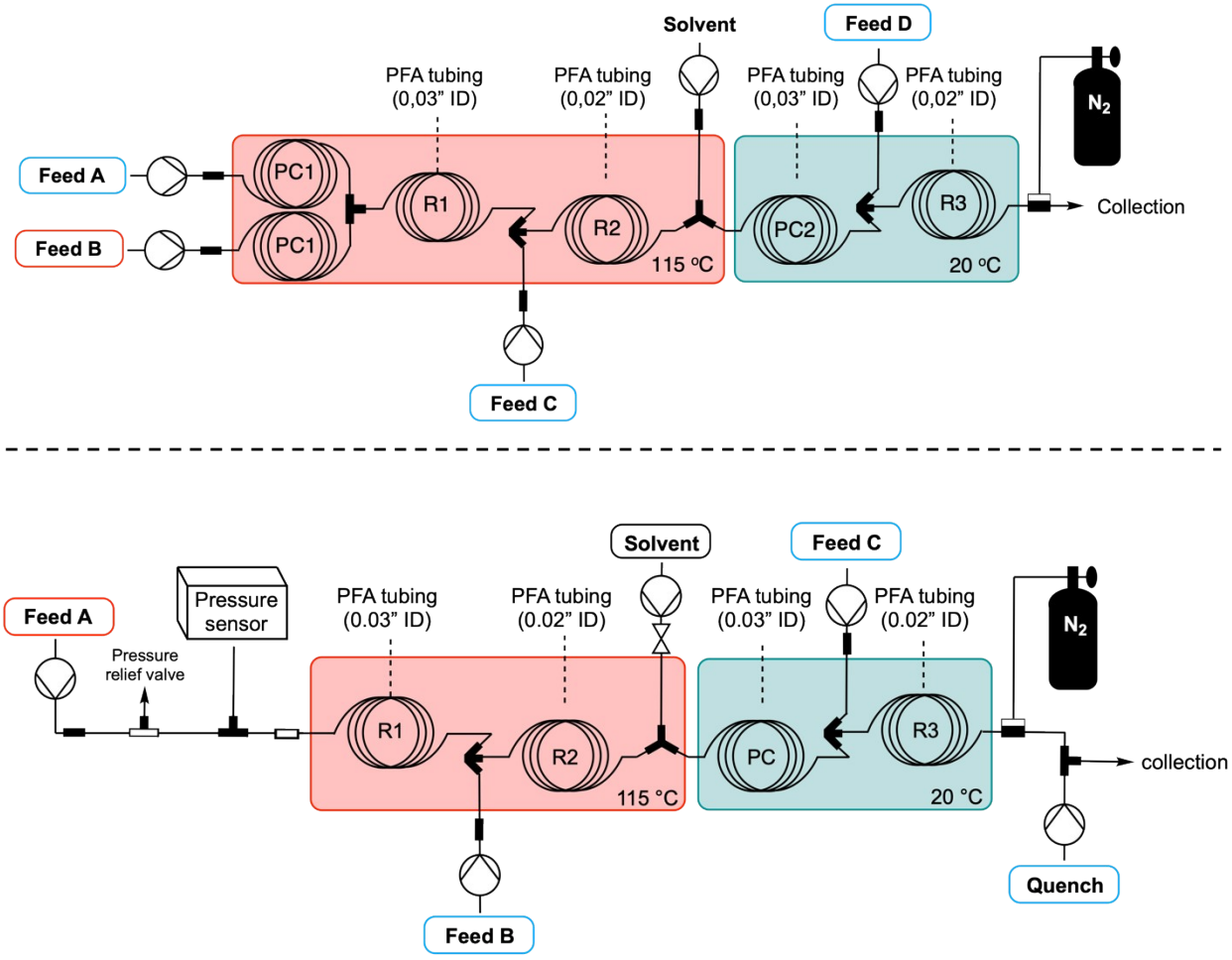
1.2. Table of Part Numbers & Vendors

Standard fluidic elements and connectors were purchased from Chrom Tech Inc./IDEX and Zaiput Flow Technologies (Table **S1**).

Table S1. Parts list for fluidic elements and connectors.

Item	Details	Reference
Connectors	SuperFlangeless™ Male Nut 1/16in PEEK	P-255
	SuperFlangeless™ Ferrule Assembly 1/16in	P-259
	FingerTight I PEEK	F-120
Unions	Union body 1/4-28 - 1/16in PEEK	P702-01
Mixers	T-mixer, natural PEEK 1/4-28 thread for 1/16" o.d. tubing, 0.02" through hole	P-712
	PEEK Y Assembly 1/4-28	P-512
	High Pressure mixing Tee UHMWPE Frit	U-466
	T-mixer, natural PEEK 1/4-28 thread for 1/16" o.d. tubing, 0.05" through hole	P-716
Check-valves	Check-valve inline cartridge 1.5 psi and cartridge holder, PEEK	CV-3000
Back pressure regulators (BPR)	Dome-type back pressure regulator (BPR)	BPR-10
Tubing	Tubing PFA High Purity 1/16” OD, 0.030” ID (50ft)	1632L
	Tubing PFA High Purity 1/16” OD, 0.020” ID (50ft)	1622L
Others	Pressure Relief Valve Assembly 100psi	U-456

1.3. Comparison of Flow Synthesis Setup (Literature[1] versus this Work)



	Feed solution kept at room temperature
	Feed solution heated to 70 °C
	Thermoregulated zones (water bath)
	Thermoregulated zones (oil bath)
	Dome-shaped back-pressure regulator
	In-line check valve
	High Pressure mixing Tee UHMWPE Frit
	T-mixer, natural PEEK 1/4-28 thread for 1/16" OD tubing, 0.02" through hole
	PEEK Y Assembly 1/4-28
	Pump

Figure S1. Top: Detailed setup for the fully concatenated continuous flow synthesis of modafinil (**1**) as reported in literature.[1] Bottom: Detailed flow synthesis setup of **1** used to concatenate with downstream continuous crystallization (CC) in this work.

Table S2. Summary of the changes made to the original setup previously reported.[1]

Original setup[1]	Issue	Modification (this work)
2-Chloroacetamide (1.5 M) and sodium thiosulfate (1.5 M) were dosed individually using two pumps. 2-Chloroacetamide solution was heated to 70 °C for solubility.	The system was vulnerable to temperature fluctuations, which resulted in precipitation of 2-chloroacetamide in the lines, with danger of clogging. Precipitation of 2-chloroacetamide resulted in less amounts of this reagent delivered. When less than stoichiometric amounts are delivered, unreacted sodium thiosulfate forms solid sulfur in contact with formic acid, resulting in clogging.	Both 2-Chloroacetamide and sodium thiosulfate were dissolved by stirring the aqueous solution at 40 °C. Having a concentration of 0.75 M of each reagent in a single solution results in the same end concentration than combining two streams at 1.5 M. This approach lowered the amount of compound that must be solubilized, without determent to the concentration of the crude.
A piston pump was used to deliver the solvent stream after R2.	Pulsations in the pump were sufficient to produce small segments of insolubilized intermediate **3**.	Dosing of the solvent was performed using a syringe pump.
Quench was performed by collecting over solid sodium sulfite.	The amount of remaining quenching reagent varies with collection time. The process was not amenable for concatenation with a continuous crystallization system.	An aqueous solution of sodium sulfate was dosed using a pump, and the mixture was collected in buffer tanks under stirring to ensure rapid mixing.
Pre-heating coils were used before R1.	This was found to be unnecessary to obtain consistent results.	Pre-coils were eliminated, resulting in a slightly shorter total residence time.

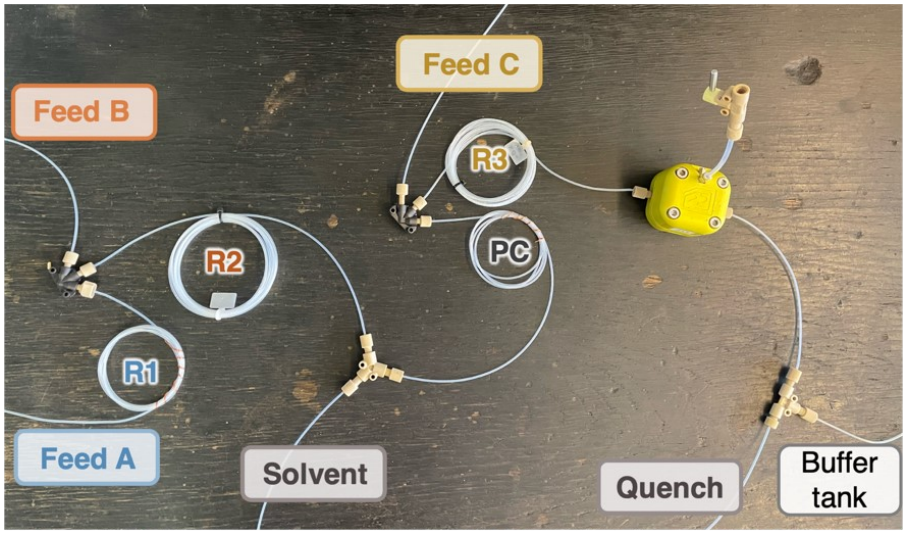


Figure S2. Photo of the reactor coils assembled for the telescoped synthesis of modafinil (**1**).

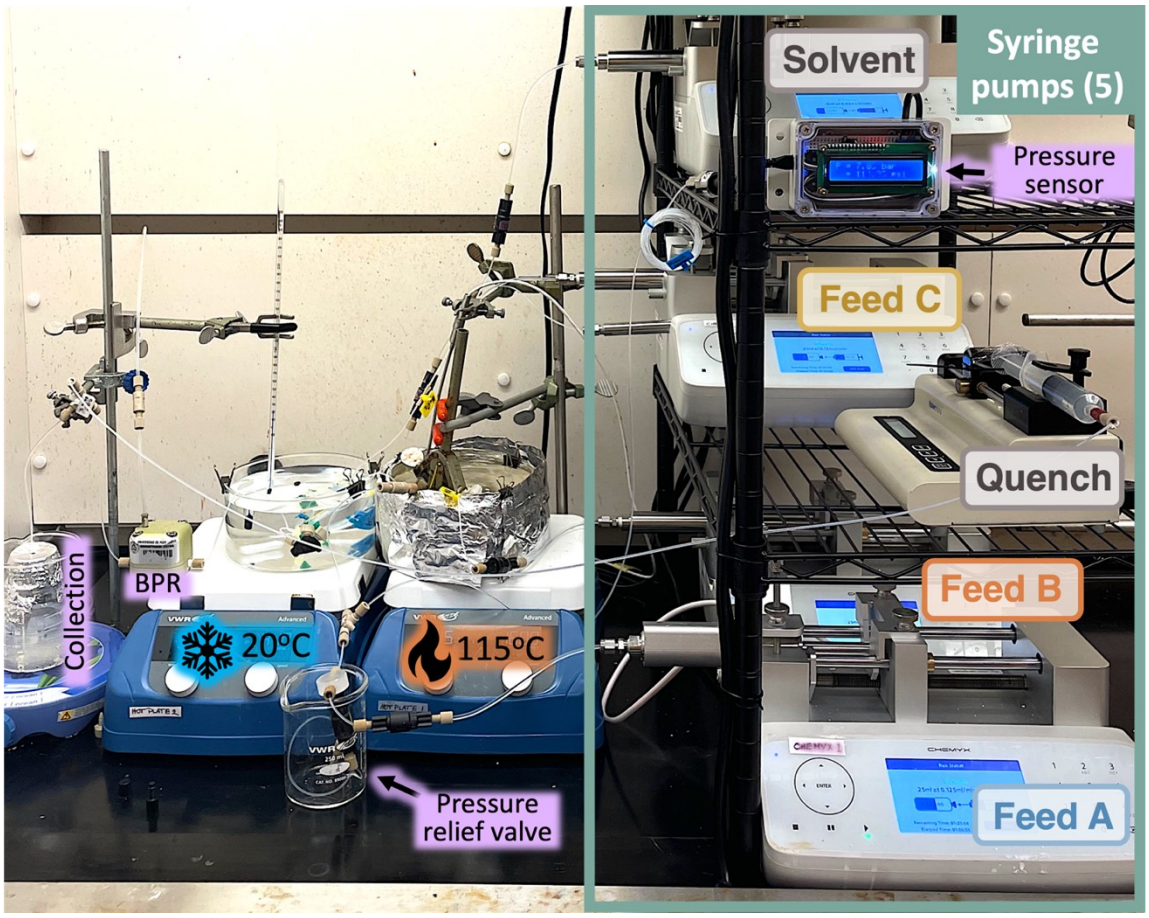


Figure S3. Photo showing the complete upstream setup for the continuous flow production of modafinil (**1**). R1 and R2 are immersed in the oil bath at 115°C, and PC and R3 are immersed in the bath at 25 °C. Pumps are labeled following the same scheme as Figure S1.

1.4. Continuous Crystallization Setup

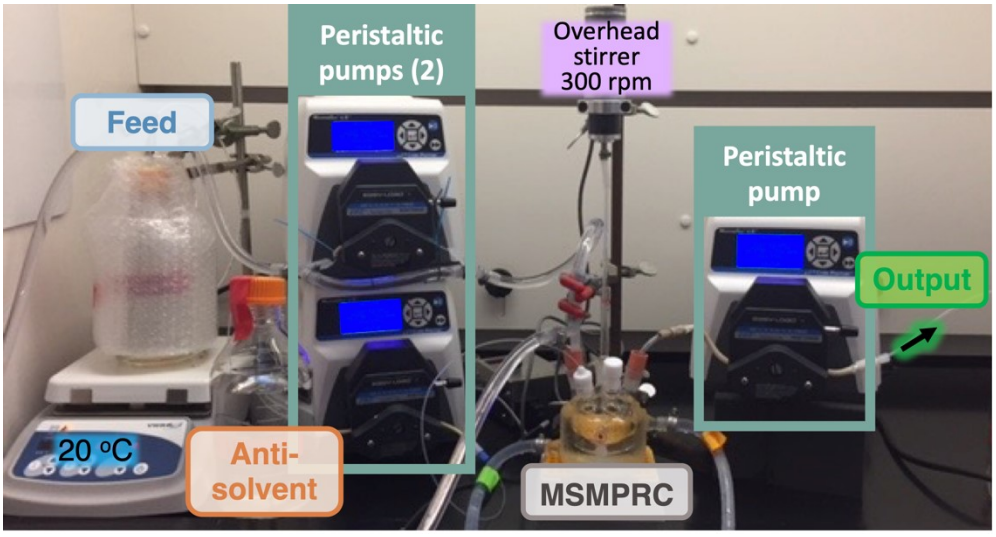


Figure S4. Photo showing the experimental setup for continuous crystallization for modafinil (**1**).

2. Additional Details on Materials

Table S3. Details on commercially purchased chemicals.

Solvents	**Purity (%)**	**CAS Number**	**Supplier**
Methylethylketone (FDA class 3)[2]	≥99.0%	78-93-3	Sigma Aldrich
tert-Butyl methyl ether (FDA class 3)[2]	≥95%	1634-04-4	Acros Organic
Formic acid (FDA class 3)[2]	98-100%	64-18-6	Merck
Chemicals	**Purity (%)**	**CAS Number**	**Supplier**
Sodium thiosulfate pentahydrate	≥99.5%	10102-17-7	Sigma Aldrich
2-chloroacetamide	=98%	79-07-2	Sigma Aldrich
Benzhydrol	99.0%	91-01-0	Sigma Aldrich
Hydrogen Peroxide	30% (w/w)	7722-84-1	Sigma-Aldrich
Sodium tungstate	ACS reagent, =99%	10213-10-2	Sigma-Aldrich
Phenylphosphonic acid	>98.0%	1571-33-1	TCI America
Sodium sulfite	BioXtra, 98%	7757-83-7	Sigma Aldrich
Modafinil (**1**)	USP, ≥99.3%	68693-11-8	Yick-Vic Chemicals & Pharmaceuticals

3. Characterization

3.1. High-Pressure Liquid Chromatography (HPLC)

An HPLC (Agilent 1100 system) equipped with a Diode-Array Detection (DAD) was used to determine the conversion and selectivity of the telescoped three-step flow synthesis process of **1** (Figure S1). HPLC conversions were determined at 220 nm wavelength as stipulated by the USP monograph.[3] The identity of the main impurities was verified with commercial standards for 2-[(diphenylmethyl)thio]acetic acid, 2-(benzhydrylthio)acetamide or with synthesized reference samples following reported procedures (see Supporting Information, section 4). The same USP HPLC method[3] was utilized for the crystallization experiments in this work to determine feed and mother liquor concentration, purity, and impurities. In this study, the column type, mobile phase, and wavelength of analysis were selected to match those proposed by the USP monograph for **1**.[3] No other USP related tests were conducted on the samples nor suitability tests or comparison with USP standards. The success criteria for purity was solely set at meeting the USP assay specification for drug substance conducted using commercial (purified) **1**.

Eluent: Isocratic

Buffer: 6.8 g L^{-1} of potassium dihydrogen phosphate in water. Adjust with phosphoric acid to a pH of 2.3.
Mobile phase: Acetonitrile and *Buffer* (40:60)
Flow: 1 mL min^{-1}
Injection Volume: 5 µL
Column: Inertsil ODS-2, 5 µm, 150 x 4.6mm
Temperature: 40 °C
Diode Array Detector: 180-800 nm

3.2. Powder X-ray Diffraction (PXRD)

PXRD was performed using a Rigaku XtalLAB SuperNova with a single microfocus Cu Kα radiation source (λ = 1.5417 Å) operated at 50 kV and 1 mA) equipped with a HyPix3000 X-ray detector in transmission mode. Powdered samples were affixed in MiTeGen microloops with a small amount of paratone oil. The diffractograms were collected at 300 K over an angular *2θ* range of 6 to 50° (step size of 0.01°) using the fast phi experiment (300 s exposure time). Data were analyzed employing the CrysAlis^{Pro} software (v 1.171.39.46).

3.3. Solubility Measurements

Adopted from literature, the polythermal method was used to determine the solubility of **1** in simulated synthesis crude solution as a function of the antisolvent (saturated sodium carbonate solution).[4,5] Specifically, an artificial solvent mixture composed of commercial MEK:FA:Water (43:35:22 v/v) was used to simulate the expected composition of the crude solution based on the synthesis protocol[1] with different amounts of antisolvent (saturated aqueous sodium carbonate solution). An automated multiple reactor system (Crystal 16, Technobis Crystallization System) was employed, as described elsewhere for **1**.[4,5] Briefly, the suspensions were prepared in 2 mL sealed glass vials (Fisher Scientific) at predetermined concentrations. To weigh the solute and the solvent, a microbalance (XP26, ±0.002 mg) and an analytical balance (MS104S, ±0.1 mg), both from Mettler Toledo, were employed, respectively. The resulting suspensions were agitated at 700 rpm using a rare earth magnetic stirring bar, while heated from 5 to 60 °C at 0.1 °C min^{-1}. Assuming the dissolution kinetics are negligible, the saturation temperature was determined at the clear point (solution is free of crystals) by monitoring the light transmission through the suspensions using the CrystalClear software (version 1.0.1.614). The measured uncertainty

of the saturated temperature is within ±0.1 K. The solubility of commercial (purified) **1** in neat and binary solvent mixtures used in this study is reported in the literature.[4]

4. Details on Flow Synthesis Procedures & Results

The feed solutions were prepared as described in Table S3. Feed A must be briefly heated to ~40 ºC to fully dissolve the compounds. Feed B must be heated to 40 ºC for 30 to 60 min to fully dissolve benzhydrol. Both feed solutions remain homogeneous after heating.

Feed solutions A and B are stable over time. However, Feed C should be prepared fresh on every occasion. Special care was taken to clean the syringe used to deliver this feed to avoid gas formation during the ~3h reaction.

Table S4. Composition of the feed solutions for the preparation of modafinil (**1**).

Feed line	**Compound**	**Solvent**	**MW** (g/mol)	**Molarity** (mol/mL)	**Volume** (mL)	**Quantity** (g)
Feed A	Sodium thiosulfate pentahydrate ($Na_2S_2O_3$)	Water	248.18	0.75	25	4.6534
	2-Chloroacetamide		93.51	0.755	25	1.7650
Feed B	Benzhydrol	Formic acid (98%)	184.23	0.6	25	2.7635
Feed C	Sodium tungstate (Na_2WO_4)	Hydrogen peroxide (15%)	329.85	0.126	10	0.4155
	Phenylphosphonic acid ($PhPO_3H_2$)		158.09	0.140	10	0.2218
In-line quenching	Sodium sulfite	Water	125.04	2	50	12.500

A scheme of the entire flow setup for the telescoped synthesis of **1** can be seen in Figure S5. The pumps used for Feeds A, B, and C were Chemyx 6000 Fusion syringe pumps equipped with 20 mL SS syringes. A Chemyx heating sleeve was attached to the syringe containing Feed A. A Fisher Scientific syringe pump 110V (Vendor Catalog # 780100I) was used to deliver the Quench feed.

The solvent composition of the crude **1** was determined by considering the solvents of all three feed solutions and the flow rates at which they are introduced in the synthesis platform.

Table S5. Calculation of the solvent composition of the crude **1** reaction mixture.

Feed line	Solvent	Flow rate (mL/ min)	Fraction of total volume
Feed A	Water	0.125	(0.125+0.0241)/0.354 = **0.421**
Feed B	Formic acid (98%)	0.125	0.125/0.354 = **0.353**
Solvent	MEK	0.08	0.08/0.354 = **0.226**
Feed C	Hydrogen peroxide (15%) (considered as water)	0.0241	(considered in the row for Feed A)

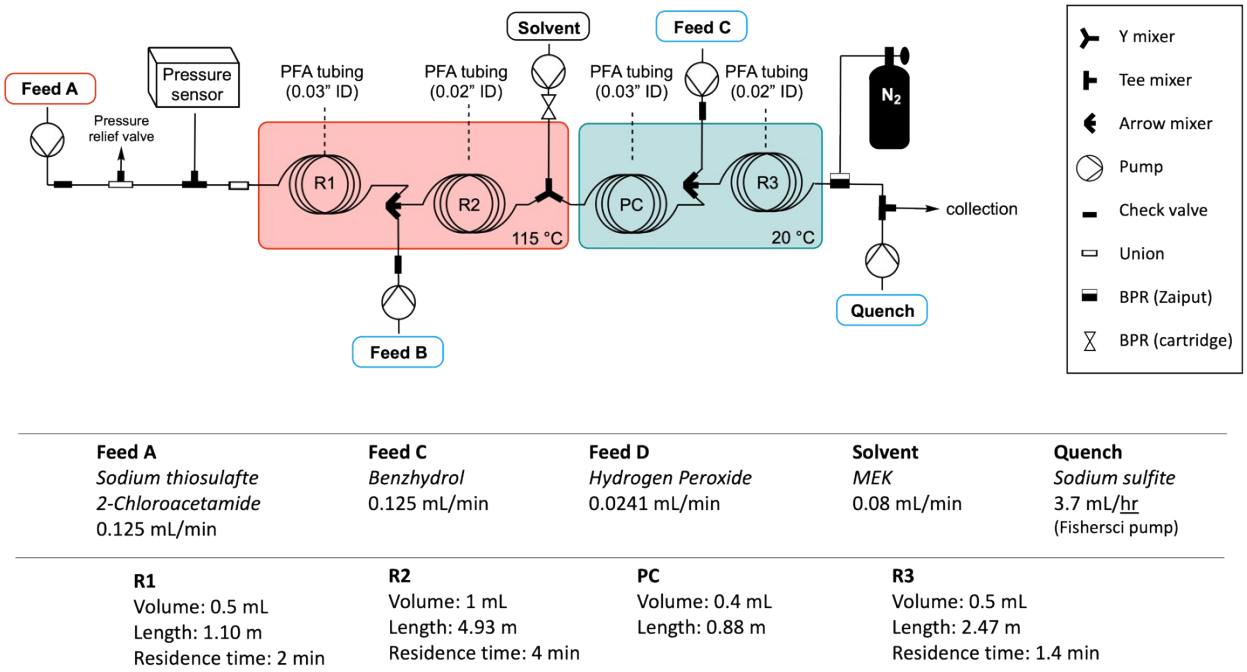


Figure S5. Scheme and details for the complete microfluidic setup for the telescoped synthesis of modafinil (**1**) in this work.

A dome-shaped back pressure regulator (Zaiput Flow Technologies) was used at the end of the concatenated PFA reaction coils to maintain the pressure at 7 bar. The T-mixer with a larger (1.25 mm) thru hole was used to connect the Quench line to the output, to decrease any chance of clogging. This output solution was collected in a vial placed in an ice bath. Stirring of this solution is essential to quickly finish quenching any remaining peroxide to avoid the formation of **6**.[1]

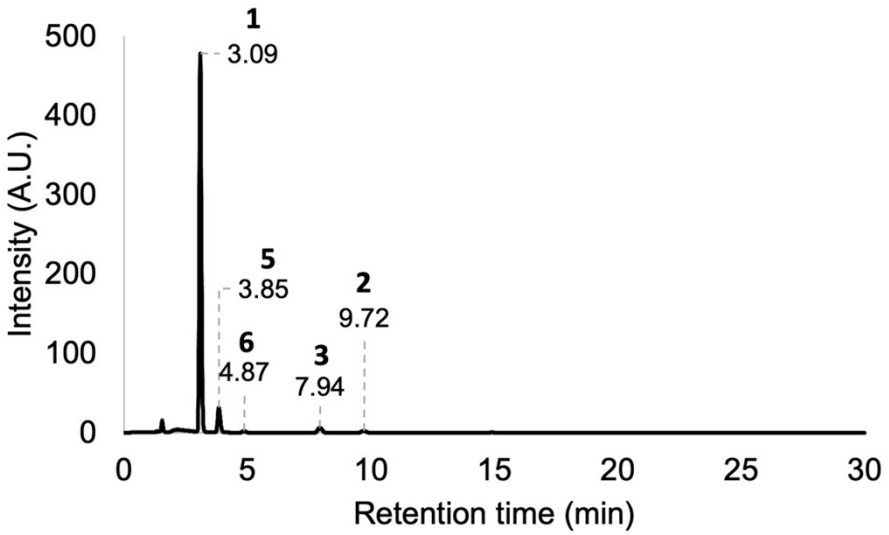


Figure S6. Representative chromatogram of a crude solution of modafinil (**1**) analyzed immediately after synthesis in the flow setup.

5. Details on Crystallization Procedures & Results

5.1. Preliminary Batch Experiments

Due to the limited amount of crude material of **1** available, in this work preliminary batch experiments were conducted to estimate the residence time for the two CC processes Cr1 and Cr2. While for the Cr2 batch screening experiments pure (commercial) **1** was used to estimate the residence time, for Cr1 crude material from the CS reaction was employed allowing to also determine the purification capacity. Briefly, for Cr1 batch screening experiments, 20 mL crude mixture of **1** was added in the crystallizer setup and kept at room temperature. Antisolvent (saturated sodium carbonate in water) was added at 0.5 mL min^{-1} under stirring to enable the rapid mixing into the solution resulting ideally in spatially uniform supersaturation levels throughout the process.[6] Every 10 min, a small aliquot (~1mL) was withdrawn and filtered through a syringe filter (0.4 μm syringe filter, Millipore). The filtrate was then immediately diluted to target and analyzed using a USP HPLC method[3] to determine the mother liquor concentration of **1**. The dried **1** crystals were also analyzed for purity.[3]

For Cr2 50 mL batch screening experiments, purified (commercial) **1** was dissolved in methanol (40 mg mL^{-1}, saturation temperature 33.9 °C)[4] by heating until all solids were visually dissolved. Thereafter, the solution was fed into the crystallizer precooled at 5 °C.

Similar to the preliminary experiments detailed for Cr1 aliquots were withdrawn periodically to determine the mother liquor concentration of **1** (via HPLC[3]) until desupersaturation was achieved.

5.2. Solubility & Supersolubility[7]

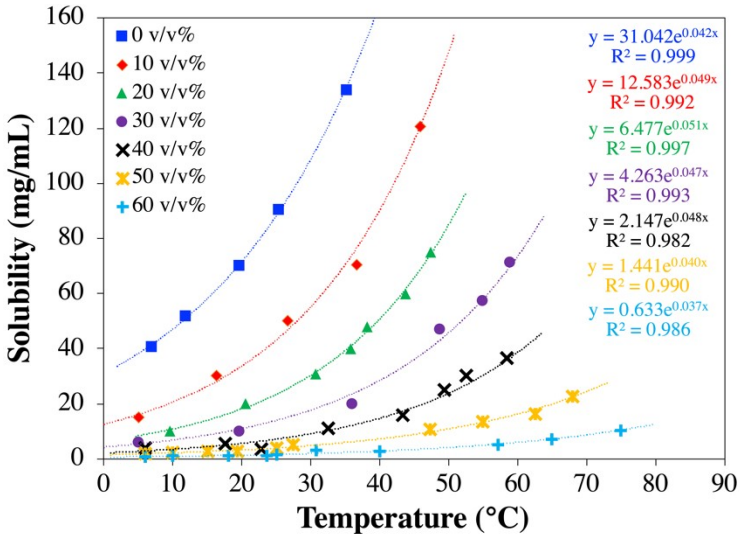


Figure S7. Scatter plot of the experimental solubility of commercial modafinil (**1**) in the ternary solvent system MEK + formic acid + water [43:35:22 (v/v/v)].

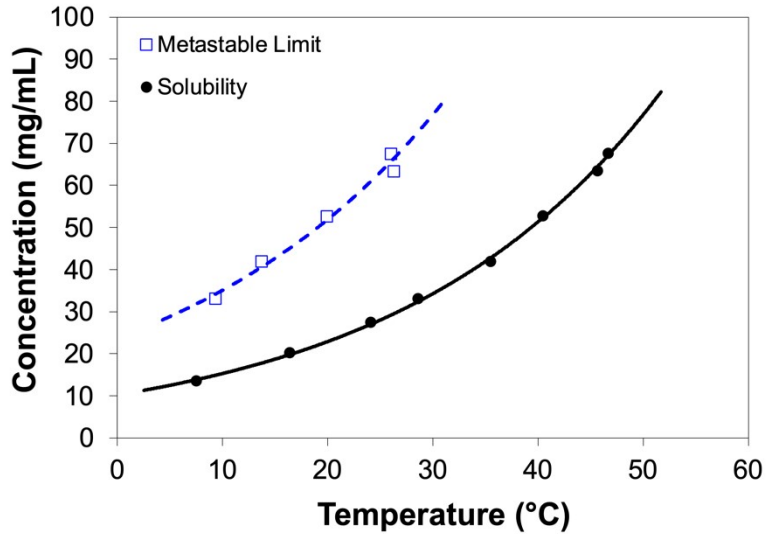


Figure S8. Solute-liquid equilibrium and metastable limit of commercial (purified) modafinil (**1**) in methanol (unpublished data extracted from preliminary solubility study reported in literature).[4]

5.3. Theoretical Yield of Cr2 Process with Antisolvent Addition and Cooling

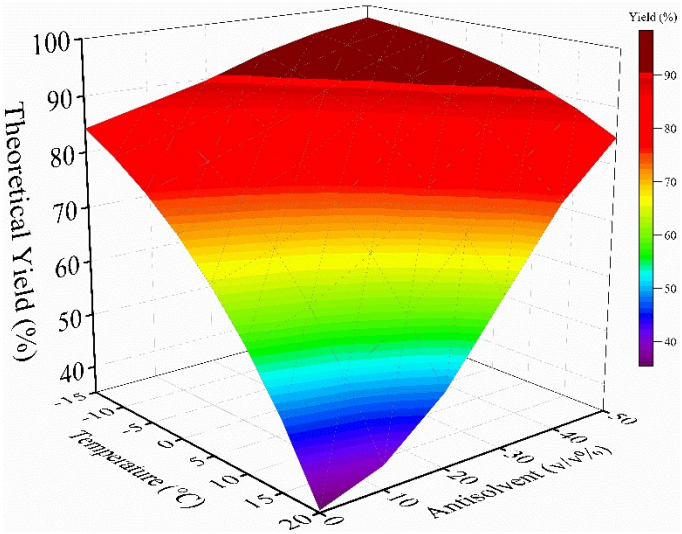


Figure S9. Surface plot for theoretical yield of modafinil (**1**) in a theoretical antisolvent cooling crystallization process as a function of temperature and antisolvent content with a feed concentration of 35.4 mg mL^{-1}.

5.4. Batch Crystallization Experiments to Mitigate Agglomeration of Modafinil

Experiments conducted with a modafinil (**1**) methanol solution saturated at 40 °C using the Crystal16 platform.

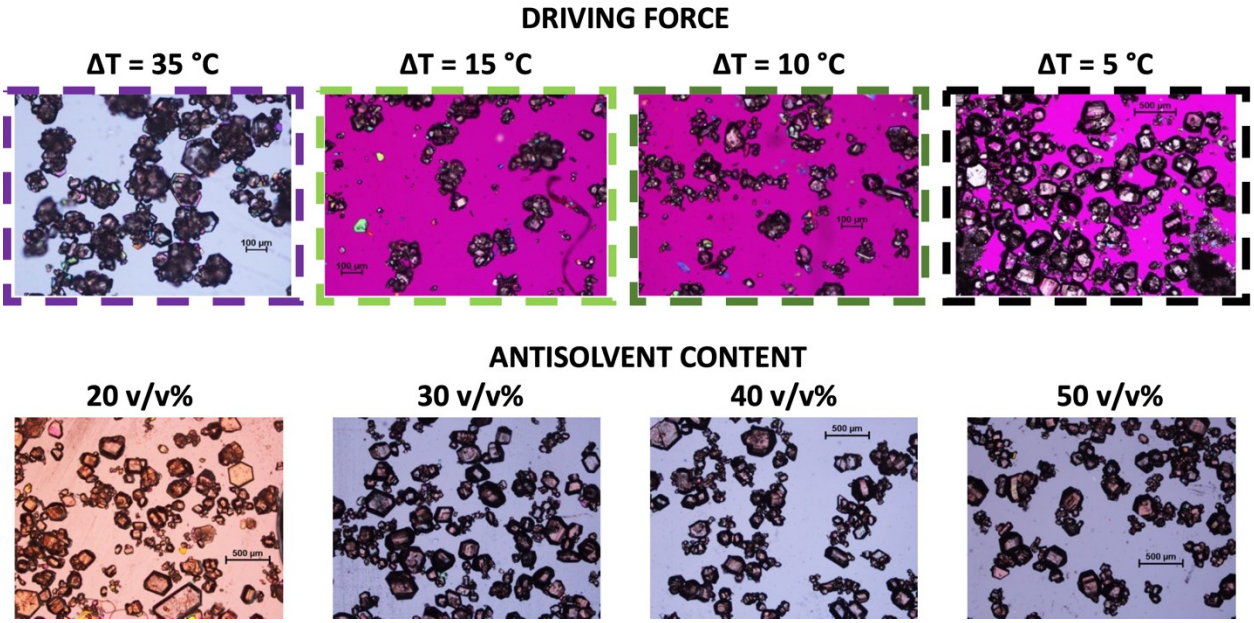


Figure S10. Impact of driving force (temperature difference to saturation temperature of 40°C) and antisolvent (water) content on the agglomeration formation of commercial (purified) modafinil (**1**) crystallized from methanol.

5.5. Continuous Cooling Crystallization (Cr2)

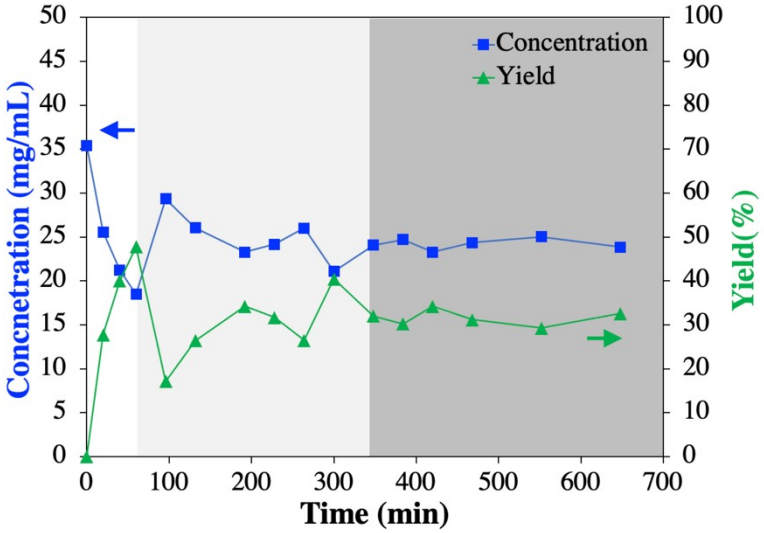


Figure S11. Progression of mother liquor concentration and yield of modafinil (**1**) during Cr2 experiment. White Zone: batch startup phase of Cr2, light gray zone: continuous operation with fluctuating signals after nucleation was visually observed, dark gray zone: Cr2 steady state.

5.6. High Pressure Liquid Chromatography (HPLC)

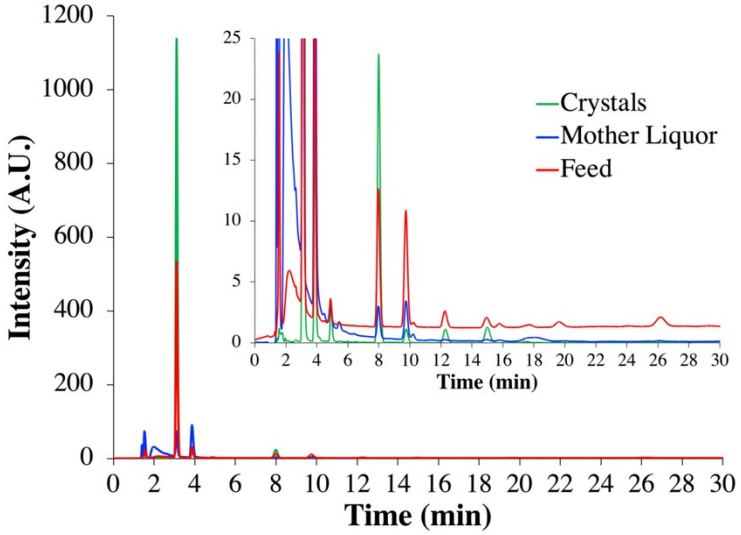


Figure S12. Representative chromatograms for batch antisolvent crystallization experiment (Cr1) at room temperature (~22 °C): Red - feed of crude modafinil (**1**) obtained from flow synthesis protocol after 4-week storage, blue - mother liquor, and green - recovered crystals of **1** after filtration at the end of the experiment. The inset shows a closer look on the smaller peaks to appreciate the minor components before and after Cr1.

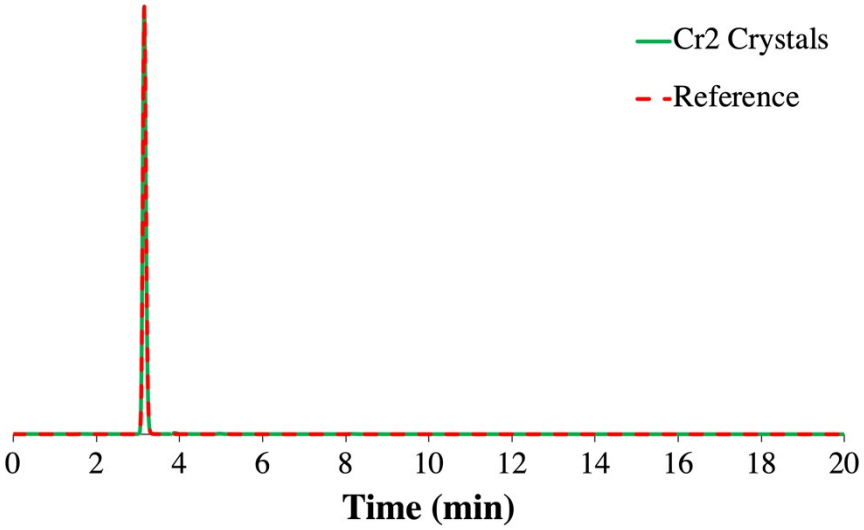


Figure S13. Normalized chromatograms of crystallized modafinil (**1**) produced from flow synthesis using the purification and separations steps described in this work (solid green line) compared to the commercial reference (dashed red line).

6. References

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