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Flow Methods

Advanced Continuous Flow Platform for On-Demand Pharmaceutical Manufacturing

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Abstract: As a demonstration of an alternative to the challenges faced with batch pharmaceutical manufacturing including the large production footprint and lengthy timescale, we previously reported a refrigerator-sized continuous flow system for the on-demand production of essential medicines. Building on this technology, herein we report a second-generation, reconfigurable and 25% smaller (by volume) continuous flow pharmaceutical manufacturing platform featuring advances in reaction and purification equipment. Consisting of two compact [0.7 (L) × 0.5 (D) × 1.3 m (H)] stand-alone units for synthesis and purification/formulation processes, the capabilities of this automated system are demonstrated with the synthesis of nicardipine hydrochloride and the production of concentrated liquid doses of ciprofloxacin hydrochloride, neostigmine methylsulfate and rufinamide that meet US Pharmacopeia standards.

Introduction

Unlike commodity chemical and petrochemical industries, which operate using an efficient continuous mode of production, pharmaceutical manufacturing has traditionally operated using a batch approach, despite the enormous space-time demand and quality-control related challenges.[1] This has been due in part to the technical complexity of active pharmaceutical ingredient (API) syntheses, coupled with the need for multiple rounds of isolation and purification to meet purity standards. Recent advancements in continuous flow technology however, have made this strategy a more practical alternative, fueling the development of highly streamlined laboratory-scale syntheses of APIs,[2] and initiating the realization of integrated, automated processes for manufacturing drug and potential drug products.[3]

In general, the benefits of continuous flow for improved chemical reaction efficiency[4] are numerous, offering the potential for decreased production times through process intensification,[5] enabling facile scale-up, and improving environmental and safety profiles and quality and consistency in production. Driven by some of these factors, Eli Lilly and Company recently developed a continuous CGMP production process for prexasertib monolactate monohydrate to be used in human clinical trials.[6] Eight continuous unit operations configured within laboratory fume hoods, enabled 3 kg of the material to be produced per day.

Previous work with colleagues at the Massachusetts Institute of Technology led to the development of a continuous automated platform for manufacturing the pharmaceutical drug aliskiren hemifumarate.[3a] The shipping container-sized unit was capable of the multi-step chemical reactions, separations,

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crystallizations, drying and formulation steps needed for the end-to-end production of tablets of this API. This work enabled us to recognize and pursue further advances in continuous manufacturing that culminated in the design of a reconfigurable system, ~1/40th the size [0.7 (L) × 1.0 (D) × 1.8 m (H)], for the on-demand synthesis and final drug product formulation of not just one, but multiple APIs.[3b] At the size of a standard North American refrigerator, this plug-and-play, first-generation reconfigurable platform succeeded in producing hundreds to thousands of liquid doses per day of diphenhydramine hydrochloride, diazepam, lidocaine hydrochloride and fluoxetine hydrochloride, each from simple starting materials. While only a proof-of-principle at this stage, an on-demand pharmaceutical manufacturing system that can be easily replicated and operated by a single end-user, offers a potential solution to the critical drug shortages[7] that often result from the challenges with batch manufacturing. Such a system could also help meet the needs of small patient populations, and provide a strategy to replace medicines with a short-shelf life, among other applications.

In seeking to further this technology, herein we present a second-generation, reconfigurable, continuous flow pharmaceutical manufacturing platform. As shown in Figures 1 a,b, this new system features stand-alone upstream and downstream units for the synthesis and the purification and formulation of APIs, respectively. It features many advances that enhance the manufacturing capabilities and also reduce the total volume of the system by more than 25% relative to the first-generation platform.[3b] These advances include a streamlined room temperature and heated reactor design and holding bay, modified compact Milligat pumps, and a custom-built in-line evaporator. Furthermore, whereas the first generation downstream unit[3b] operated purely in batch mode for isolations and purifications, this next generation system includes continuous processing for crystallization[8] and semi-continuous filtration, washing, dispensing and drying.

To showcase the capabilities of this platform by highlighting a variety of unit operations, the continuous synthesis of nicardipine hydrochloride (**1**) (antihypertensive drug) and the manufacturing of concentrated liquid doses of ciprofloxacin hydrochloride (**2**) (antibiotic), neostigmine methylsulfate (**3**) (muscle strengthener) and rufinamide (**4**) (anticonvulsant) that meet United States Pharmacopeia (USP) standards are demonstrated (Figure 1 c). While we have previously developed flow strategies to synthesize two of these APIs, namely ciprofloxacin hydrochloride[9] and rufinamide[10] in their crude forms and on the milligram scale, this is the first demonstration of their end-to-end manufacturing into oral liquid doses that meet USP standards within such a platform.

Results and Discussion

Upstream unit

The self-contained upstream unit has a frame dimension of 0.7 (L) × 0.5 (D) × 1.3 m (H) and consists of three compact modules housing the operations required for the synthesis of the APIs including the reaction-based equipment and controls (i.e. reaction module), the pumps (i.e. pump module) and reaction solvents (i.e. solvent module) (Figure 1 a). A custom LabVIEW

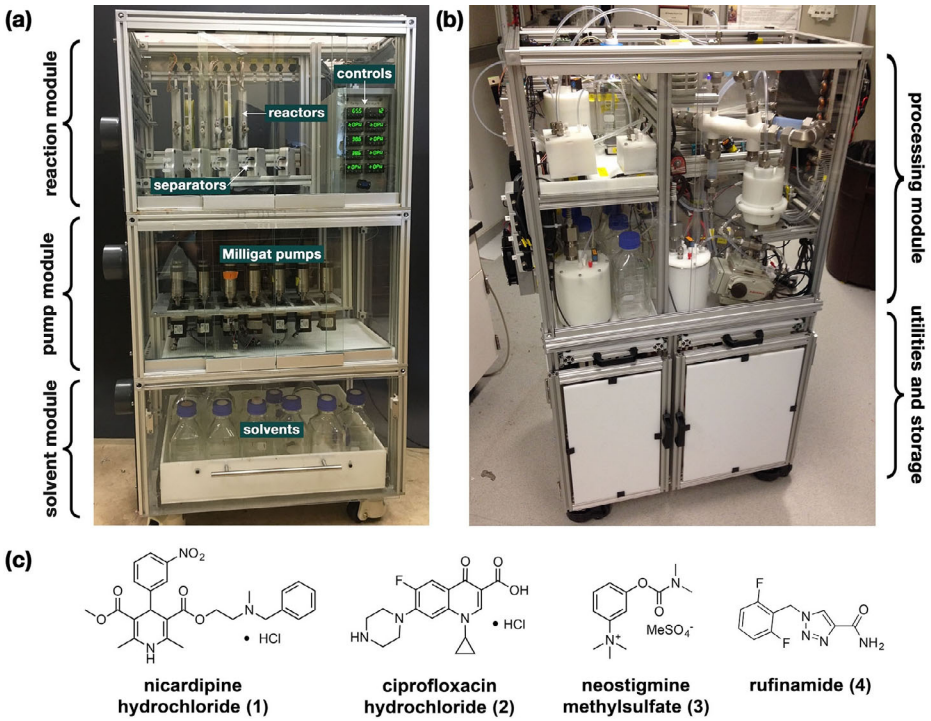

Figure 1. Labelled photographs of the a) upstream unit for the synthesis and b) downstream unit for the purification and formulation of the APIs. c) Four APIs synthesized in the platform.

interface is used to coordinate the pumps and temperature control as well as monitor the pressure and temperature throughout the synthesis and capture in a data file.

The reaction module shown in Figure 1a contains ten bays for holding process reactors capable of operating at room temperature or under thermal conditions. The custom-designed reactors use disposable perfluoroalkoxy alkane (PFA) tubing that can be readily replaced to prevent cross-contamination between API production runs. Figure 2a shows the 3D printed

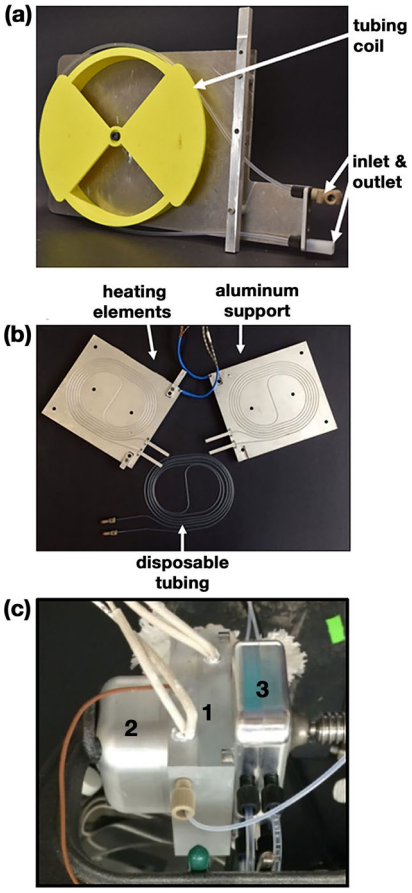

Figure 2. Photographs of the a) room temperature reactor, b) heated reactor and c) in-line evaporator. The heat exchanger, BPR and membrane-based separator in the in-line evaporator are indicated in (c) by 1–3, respectively.

reel of the room temperature reactor whereby the PFA tubing (volume from 500 μL–10 mL) is coiled onto an aluminum backing plate. The heated reactors (5 and 10 mL) alternatively, consist of an aluminum shell, silicone insulation and a thin-walled PFA tubular liner to improve heat transfer into the process stream (Figure 2b). The aluminum shell not only provides uniform heating, but also supports the tubing at high temperatures and pressures as the yield strength of PFA exponentially declines with increasing temperature. Reactor heating is accomplished through the use of embedded cartridge heaters.

In addition to the reactors, the reactor module also holds 20 auxiliary devices such as the custom-built in-line evaporator, flow meter, pressure sensors and separators.[3b] The in-line evaporator shown in Figure 2c, was designed with operating principles similar to those previously described[11] and is suitable for a liquid flow rate up to 5 mL min^{-1}. It combines a heat exchanger, back pressure regulator (BPR) and membrane-based separator[3b] into one device and operates by heating the incoming fluid stream under pressure to a temperature above the boiling point of the solvent to be removed. The stream experiences a pressure drop as it passes through the BPR and flash evaporates to a gas-liquid mixture. The vapor is then separated from the fluid stream with the use of the in-line gas-liquid separator.

Along with the reactor module, the upstream unit also features a pump module for operating 21 modified Milligat pumps capable of withstanding high pressures and continuous operation (Figure 1a). Lastly, a ventilated solvent module is incorporated in the upstream unit for holding 10×1 L and 13×500 mL solvent bottles.

Downstream unit

The downstream unit shown in Figure 1b and Figure S3, consists of a processing module (top) along with utilities and storage (bottom) within a frame having dimensions of 0.7 (L)×0.5 (D)×1.3 m (H). Within the processing module, separation and purification operations are performed on the crude API liquid stream delivered from upstream, to generate the solid drug substance, which is then formulated into liquid doses. The system achieves these operations using a number of custom-designed units including a precipitation unit (Figure 3a), batch and continuous crystallization units (Figure 3b), formulation/feed tank units (Figure 3c) and a filter-washing drying unit (FWD) (Figure 3d). Automation is achieved using a LabVIEW interface with the exception of liquid coolers and magnetic stirrers which are hardware controlled.

Notably, continuous crystallization is realized in this second generation system using the pressure driven flow crystallization (PDFC) unit shown in Figure 3b. It is designed to perform a single or two-stage crystallization process using jacketed temperature-controlled continuous stirred tank reactors (CSTRs) with 30–180 mL working volumes. Feed and antisolvent streams are continuously fed into these units and the resulting product stream is intermittently withdrawn and pumped into the FWD unit shown in Figure 3d. The FWD unit vacuum filters the solid product from the mother liquor, washes the product over the filter and then pneumatically transfers and dispenses the product to a collection chamber for additional drying. Once a batch has been collected and dried in the collection chamber, formulation solvent can be added to dissolve or suspend (in the case of a suspension formulation) the product prior to transfer to the formulation tank (Figure 3c) for further concentration adjustment if needed. The formulation unit consists of a jacketed temperature controlled vessel with a level sensor, a suspended magnetic stirrer for mixing and a single frequency ultrasound (SFU) probe in place for determining solution concentration.

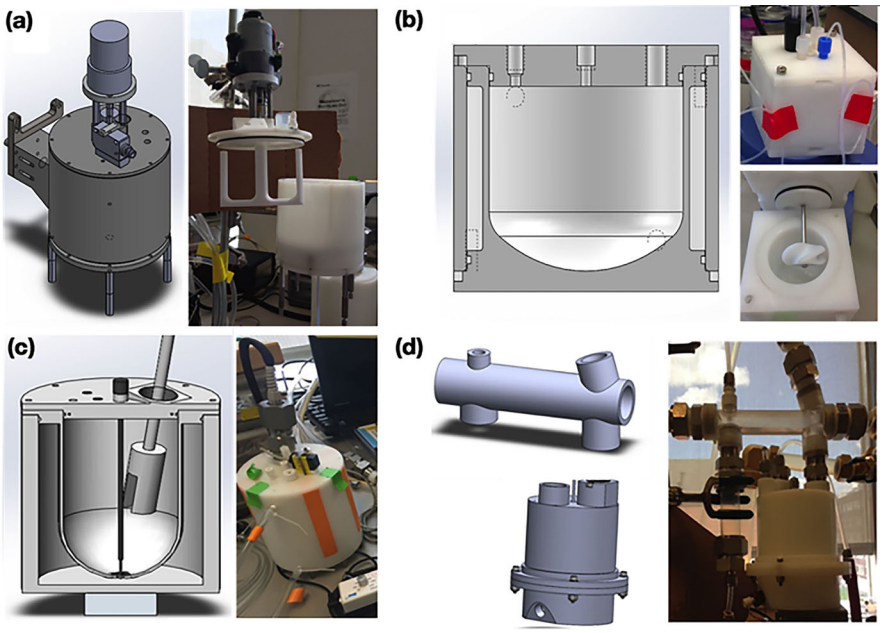

Figure 3. Overview of the custom-designed downstream system components. a) Precipitation unit with filter in base. b) Pressure-driven flow crystallizer. c) Feed tank/formulation tank design. d) FWD unit with collection chamber.

API synthesis

As shown in Figure 4, the capabilities of the upstream unit were first demonstrated with the synthesis of a crude solution of nicardipine hydrochloride (**1**). Neat *N*-benzyl-*N*-methylethanolamine (**5**) was reacted with neat 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**6**)[12] in Reactor I at 120 °C at a pressure of 0.97 MPa via the use of a BPR.[3b] After a residence time of 60 min, the resulting intermediate **7** was then mixed with a stream of 3-nitrobenzaldehyde (**8**) and methyl 3-amino-2-butenoate (**9**) in the presence of 10% piperidine and 10% acetic acid in a mixture of *i*PrOH and CH_2Cl_2. After flowing through Reactor II for 20 min at 120 °C to promote the condensation reaction, the crude nicardipine underwent in-line acidification followed by a purification/extraction process with the aid of two separate mixing tubes to increase mass transfer and two membrane-based liquid-liquid separators. The resulting nicardipine hydrochloride (**1**) was provided in 43% yield as a solution in DMSO and H_2O and at a production capacity of 3150 doses per day. Due to the tendency of the API to oil-out and form amorphous solids during the batch precipitation and recrystallization studies,[13] downstream processing in the frame was not carried out in the interest of time. Regardless, this work demonstrated the use of elevated pressure (0.97 MPa) and temperature (120 °C) in the frame, enabling complete conversion of the starting materials to the crude API in just 80 min.

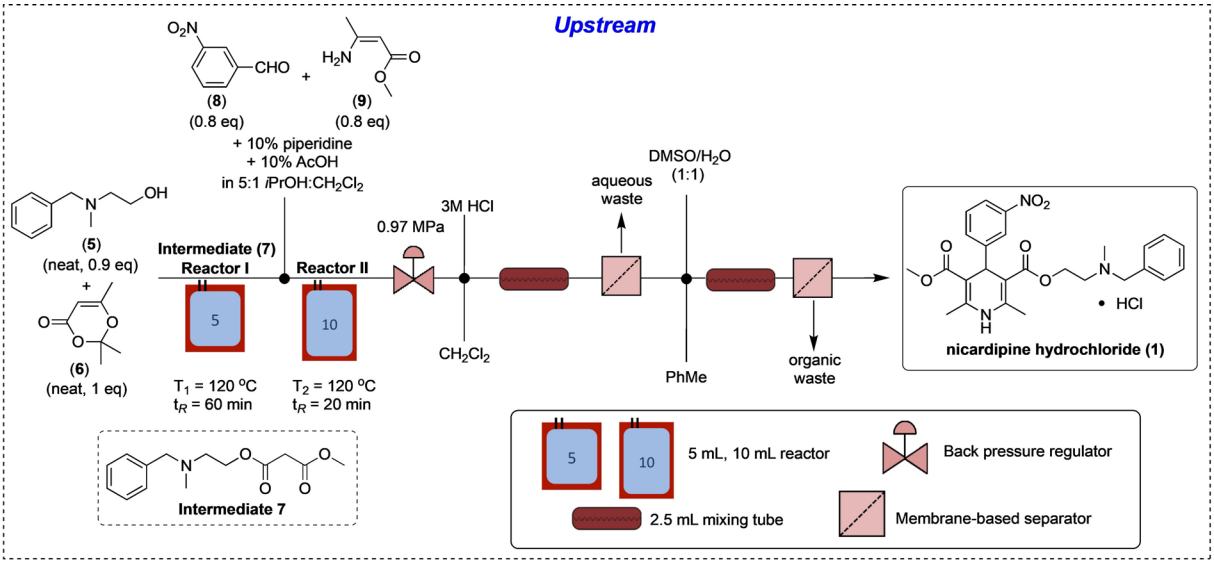

Figure 4. Upstream synthesis of nicardipine hydrochloride (**1**).

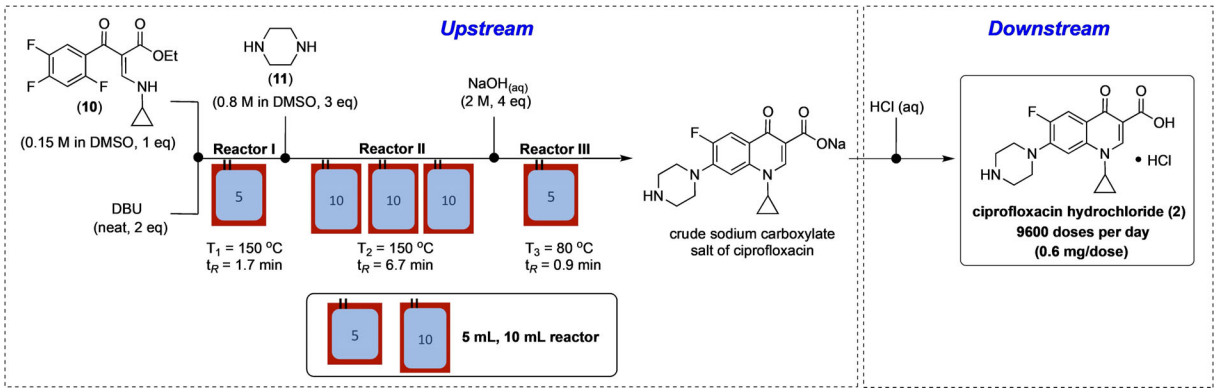

Figure 5. Upstream and downstream manufacturing of ciprofloxacin hydrochloride (**2**) starting from intermediate **10**.[14]

Following the upstream synthesis of **1**, we next transitioned to the end-to-end manufacturing of ciprofloxacin hydrochloride (**2**). As shown in Figure 5, the upstream synthesis commenced by merging a stream of excess 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with intermediate **10**.[14] After flowing through Reactor I for 1.7 min at 150 °C, a solution of piperazine (**11**) in DMSO was added and the combined mixture was heated to 150 °C in a 30 mL reactor constructed using three sequential 10 mL reactors. After a residence time of 6.7 min, an aqueous NaOH solution was added and the combined mixture was flowed through Reactor III for 0.9 min at 80 °C. The sodium carboxylate salt of ciprofloxacin was provided in 86% yield as a solution in DMSO and H_2O. Overall, this crude material was produced from **10** in only 9.3 min compared to other reported protocols which require many hours starting from similar intermediates.[15]

For the downstream processing, the API was first precipitated with 0.1 M HCl, filtered, washed and then redissolved in 0.25 M HCl prior to a continuous antisolvent crystallization using acetone. The crystal suspensions were then processed in the FWD unit, and transferred into a collection chamber and held for 1 h at 60 °C prior to dissolving in the water formulation solvent (Table S5). Real-time monitoring using an SFU probe provided a final concentration of 1.5 mg mL^{-1}. HPLC analysis (Figure S6) resulted in a 98.2% purity for **2** and thus conformed to USP standards.[16] Overall, 2700 doses of **2** were produced (3.5 mg mL^{-1} solution, 1 drop per eye, 0.6 mg per dose). After start-up and reaching steady state (6.8 h) this corresponds to a production rate of 9600 doses per day.

The third API manufactured was neostigmine methylsulfate (**3**) (Figure 6). The upstream synthesis of **3** began by mixing a solution of 3-(dimethylamino)phenol (**12**) and 18-crown-6 in DMF with a stream of KO*t*Bu in THF. After a residence time of 3.5 min at 40 °C in Reactor I, a solution of dimethylcarbamoyl chloride (**13**) in THF was added and the mixture was heated in Reactor II (spiral-type[3b]) for 30 s at 40 °C to facilitate the acylation reaction. Two in-line extraction and separation steps with the aid of membrane-based separators[3b] provided the acylated adduct as a solution in toluene. Subsequent solvent evaporation via the in-line evaporator, yielded a ≈30% more concentrated solution that was then treated with a stream of dimethyl sulfate as a 5 M solution in toluene. After heating in Reactor III at 95 °C for 5.5 min, **3** was provided as a crude solution in toluene in 54% yield.

For the downstream processing, ethanol was first added to the crude suspension of **3** to generate a homogeneous solu-

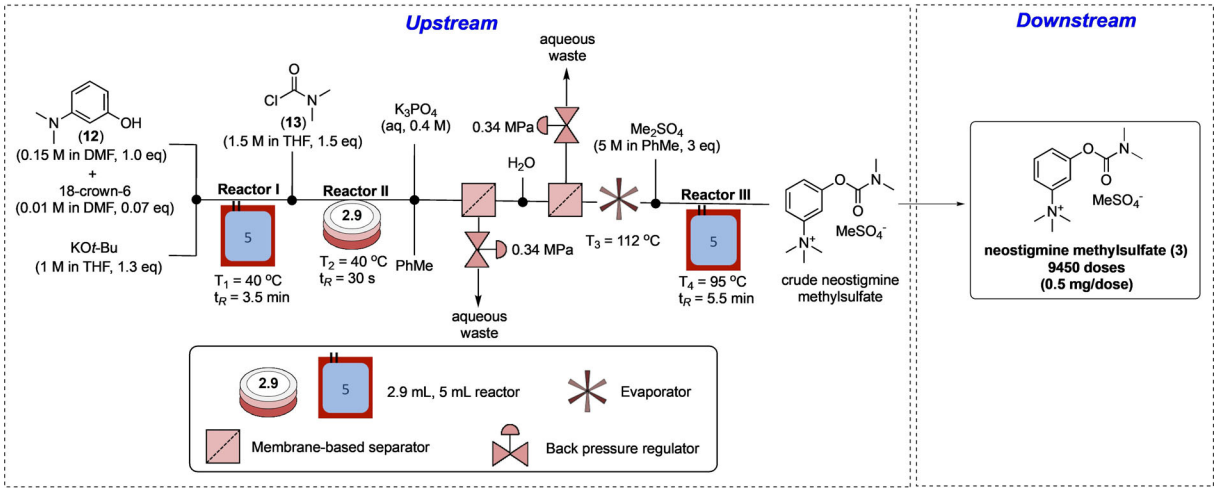

Figure 6. Upstream and downstream synthesis of neostigmine methylsulfate (**3**).

tion. The API was then precipitated with methyl *tert*-butyl ether (MTBE), filtered and dissolved in ethanol under batch conditions to remove the residual dimethyl sulfate. The resulting feed solution was next precipitated, filtered, washed and dried in the downstream unit prior to a continuous antisolvent crystallization using MTBE. After repeating the batch precipitation and continuous crystallization process, crystal suspensions of sufficient purity were provided, which were then processed through the FWD unit. The dried solids, which met USP standards (Figure S10),[17] were dissolved in the water formulation solvent to provide a final concentration of **3** of 1.1 mg mL^{-1} as determined using a SFU probe (Table S5). To accommodate the batch processing of **3** in the downstream process, further optimization is required. Although a production rate cannot be accurately determined, 9450 liquid doses (0.5 mg/dose) of **3** were successfully produced.

The final API manufactured was rufinamide (**4**). As detailed in Figure 7, a convergent strategy was implemented whereby energetic benzyl azide **15** was produced in situ to avoid handling. It was then consumed in a [3+2] cycloaddition reaction with propiolamide (**17**), a polymerization-prone[18] intermediate also generated in situ. The synthesis of the requisite azide **15** was accomplished by merging a solution of **14** in DMSO with excess sodium azide in DMSO in Reactor I for 7 s at room temperature. Propriolamide (**17**) was separately generated by reacting neat methyl propiolate (**16**) with an aqueous solution of ammonia in Reactor II at room temperature for 5.9 min. After merging the two solutions, the mixture was treated with an aqueous solution of sodium ascorbate followed by a premixed aqueous solution of $Cu(OAc)_2$ and 1,10-phenanthroline in catalytic quantities. Heating in Reactor III for 6.8 min at 80 °C under elevated pressure (0.69 MPa) provided **4** in 77% yield as a crude solution in DMSO and water.

The downstream processing commenced by precipitating **4** using an aqueous solution of ethylenediaminetetraacetic acid (EDTA) and NaOH at 50 °C. Following filtration and washing, the solids were re-dissolved in DMSO prior to a continuous antisolvent crystallization using EDTA/NaOH. The crystal suspensions were then filtered and washed with a mixture of acetone and water prior to being held in the collection chamber at 60 °C for 24 h. HPLC analysis revealed the resulting rufinamide crystals had a 99.4% purity and thus met USP standards (Figure S13).[16] Redissolution in the formulation solvent (0.1% poloxamer) provided a final concentration of 40.4 mg mL^{-1} (Table S5). In total, 20 doses of rufinamide (**4**), each dose corresponding to 200 mg (5 mL of 40 mg mL^{-1} suspension/dose) were manufactured. After start-up and reaching steady state (4.5 h) this corresponds to a production rate of 75 doses per day.

Conclusion

In summary, a reconfigurable, continuous flow platform featuring custom-designed unit operations has been developed for on-demand manufacturing of liquid formulations of APIs. Among the advancements in this second-generation system is an in-line evaporator, which was implemented in the upstream synthesis of neostigmine methylsulfate (**3**). Streamlined room temperature and heated reactors have also been developed that fit within standardized bays within the reactor module in the upstream unit. In addition to having a more compact design, the PFA tubing within these reactors can be readily replaced as part of the facile switching process between API production runs. Other innovations in this system include the incorporation of continuous processing operations for crystallization[8] and semi-continuous filtration, washing, dispensing and drying.

To increase the throughput of APIs such as rufinamide which have large prescribed doses (200 mg), future considerations may include the scale-up of custom vessels or operating multiple units in parallel. For example, based on the current crystallization process, increasing the working volume from 60 mL to 350 mL per crystallizer would deliver approximately 1200 doses of **4** per day. Crystallizers with this larger volume are projected to fit within the current downstream module.

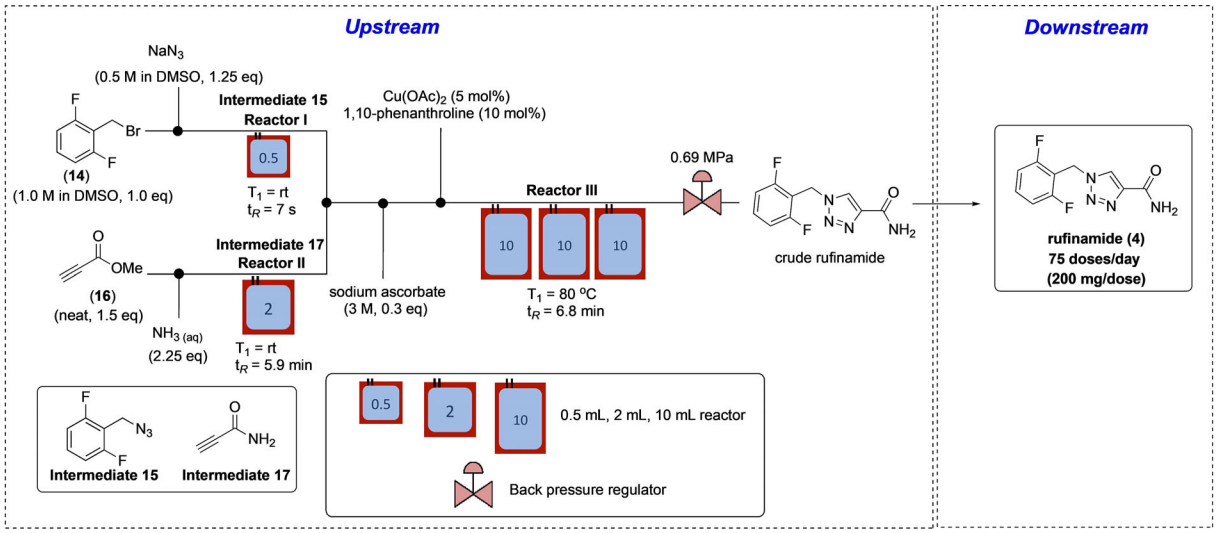

Figure 7. Convergent upstream synthesis and downstream processing of rufinamide (**4**).

Experimental Section

Additional details of the platform and synthesis and characterization (NMR, XRPD and HPLC) data can be found in the Supporting Information.

General methods: All reagents and solvents were purchased from commercial suppliers and used as received, unless otherwise noted. Deionized (DI) water was obtained from a Milli-Q, Millipore system. NMR analysis was performed on a JEOL JNM-ECZR 500 MHz spectrometer in the specified deuterated solvent. The ^{1}H NMR data is reported as follows: chemical shift in parts per million (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz) and integration. X-ray powder diffraction was performed on all samples using a PANalytical X'Pert PRO diffractometer at 45 kV with an anode current of 40 mA. The instrument has a PW3050/60 standard resolution goniometer and a PW3373/10 Cu LFF DK241245 X-ray tube. Samples were placed on a spinner stage in reflection mode. Settings on the incident beam path included soller slit 0.04 rad, mask fixed 10 mm, programmable divergence slit and fixed 1° anti-scatter slit. Settings on the diffracted beam path include: soller slit 0.04 rad and programmable anti-scatter slit. The scan was set as a continuous scan: 2θ angle between 4° and 40°.

Nicardipine hydrochloride (1)

Upstream synthesis of 1: Premixed *N*-benzyl-*N*-methylethanolamine (**5**) (neat, 0.9 equiv.) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**6**) (neat, 1.0 equiv.) were pumped (0.08 mL min^{-1}) through Reactor I (5 mL reactor, 2 mm inner diameter) for a residence time of 60 min at 120 °C. The resulting ester was then treated with a stream (0.42 mL min^{-1}) of 3-nitrobenzaldehyde (**8**) (0.48 M, 0.8 equiv.), methyl 3-amino-2-butenoate (**9**) (0.8 equiv.), 10% piperidine and 10% acetic acid in a 5:1 mixture of isopropanol and dichloromethane. The combined reaction stream was heated to 120 °C in Reactor II (10 mL reactor) for 20 min and passed through a 0.97 MPa back pressure regulator. A solution of HCl (3 M, 1.4 mL min^{-1}) and dichloromethane (0.29 mL min^{-1}) was subsequently introduced and the resulting mixture was flowed through a 2.5 mL mixing tube, followed by a membrane based liquid-liquid separator. The product was treated with a 1:1 stream of dimethyl sulfoxide (0.86 mL min^{-1}) and water (0.29 mL min^{-1}) and passed through a second 2.5 mL mixing tube, followed by a membrane based liquid–liquid separator to provide nicardipine hydrochloride (**1**) in 43% yield as a solution in dimethyl sulfoxide and water. ^{1}H NMR of the crude free base (500 MHz, CD_3CN): δ = 8.07 (t, J = 2 Hz, 1H), 7.95 (ddd, J = 8.3, 2.4, 1.1 Hz 1H), 7.70–7.68 (dt, J = 7.8, 1.4 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.29–7.20 (m, 5H), 5.07 (s, 1H), 4.12 (t, J = 5 Hz, 2H), 3.57 (s, 3H), 3.53–3.43 (m, 2H), 2.63–2.54 (m, 2H), 2.30 (s, 3H), 2.29 (s, 3H), 2.13 ppm (s, 3H). ^{13}C NMR of the crude free base (125 MHz, $CDCl_3$) δ = 167.6, 167.1, 149.7, 148.4, 145.3, 145.2, 138.7, 134.5, 129.0, 128.8, 128.3, 127.2, 122.9, 121.5, 103.2, 62.6, 61.8, 55.6, 51.2, 42.3, 39.7, 19.73, 19.67 ppm. HRMS (ESI+) *m/z* calcd for $C_{26}H_{29}N_3O_6H^+$ $[M+H]^+$: 480.2129; found: 480.2127.

Ciprofloxacin hydrochloride (2)

Upstream synthesis of 2: Ester **10** (0.15 M in DMSO, 1 equiv.) (2.8 mL min^{-1}) was mixed with excess DBU (neat, 2 equiv.) (118 μL min^{-1}) and flowed through Reactor I (5 mL reactor) at 150 °C for a residence time of 1.7 min. The outflow was then treated with a stream of piperazine (**11**) (0.8 M in DMSO, 3 equiv.) (1.58 mL min^{-1}) and pumped through Reactor II (a 30 mL reactor assembled from three 10 mL reactors connected sequentially) at 150 °C. After a residence time of 6.7 min, the outflow was mixed with a stream of aqueous NaOH (2 M, 4 equiv.) (0.84 mL min^{-1}) and flowed through Reactor III (5 mL reactor) at 80 °C for a residence time of 0.9 min. The sodium carboxylate salt of ciprofloxacin was collected and provided in 86% yield as a solution in DMSO and H_2O.

Downstream processing of 2

Precipitation: The crude solution from the upstream synthesis was neutralized using HCl (0.1 M) at a ratio of crude solution:0.1 M HCl of 1:4.5. The crude solution (29.3 mg mL^{-1}) was pumped into the buffer tank until the desired volume was reached (400 mL) and to this, HCl (0.1 M, 600 mL) was added. The diluted crude was then processed in 3 batches through the precipitation tank with the addition of HCl (0.1 M) to complete the neutralization. Each batch was aged for 20 min before pumping into the precipitation unit for filtration and washing. Solids were washed with water before holding the system under vacuum for 10 min. The washed solid was dissolved in HCl (0.25 M) under agitation for 20 min before pulling the generated API salt solution into the crystallization feed tank. Details of the solvent volumes are provided in the Supporting Information in Table S1. A sample of the API solution was removed from the feed tank to assess the concentration. HPLC analysis (data not shown) provided a concentration of 35.2 mg mL^{-1}. The resulting yield of this process was 67%.

Continuous crystallization: The continuous antisolvent crystallization was carried out using acetone at a solvent:antisolvent ratio of about 10:90. The feed solution and acetone were pumped into the first stage CSTR at 0.49 and 4.6 mL min^{-1}, respectively. Details regarding the crystallization volumes and process parameters are provided in the Supporting Information in Table S2. The agitation rate at each stage was 600 rpm. The resulting yield of ciprofloxacin hydrochloride (**2**) from this process was 32%.

Filtration, washing, drying and formulation: Crystal suspensions were processed in the FWD at 2 mL min^{-1} (30 mL aliquots per 15 min FWD cycle). The filtered material was washed with acetone (10 mL) before vacuum drying for 10 min. Solids were then transferred into the collection chamber for further drying. In total, 7 aliquots were filtered, washed, dried and dispensed from the FWD unit. A manual sample taken from the collection chamber before further drying resulted in a TGA analysis of 93.7% solids. Solids were held in the collection chamber for 60 min with the heating tape set to 60 °C (note that the heating tape applied to the outside of the FWD collection chamber is not shown in Figure 3 or Figure S3). Formulation solvent (300 mL of water) was pumped into the collection chamber with agitation before transferring into the formulation tank. The resulting concentration of the ciprofloxacin hydrochloride (**1**) solution was 1.5 mg mL^{-1}. In total, 1.62 g of ciprofloxacin hydrochloride was produced corresponding to 2700 doses (3.5 mg mL^{-1} solution, 1 drop for each eye, 0.6 mg per dose). After start-up and reaching steady state, this corresponds to a production rate of 9600 doses per day. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 15.11 (s, 1H), 9.38 (s, 2H), 8.67 (s, 1H), 7.94 (d, J = 13.0 Hz, 1H), 7.59 (d, J = 7.3 Hz, 1H), 3.85 (m, 1H), 3.55 (t, J = 4.8 Hz, 4H), 3.28 (overlap with solvent, 4H), 1.30 (t, J = 6.5 Hz, 2H), 1.18 ppm (t, J = 5.1 Hz, 2H). ^{1}H NMR (500 MHz, D_2O) δ = 8.43 (s, 1H), 7.36 (d, J = 7.0 Hz, 1H), 7.19 (d, J = 12.7 Hz, 1H), 3.68–3.53 (m, 5H), 3.49 (t, J = 4.8 Hz, 4H), 1.39 (d, J = 7.0 Hz, 2H), 1.12 ppm (bs, 2H). ^{13}C NMR (126 MHz, D_2O): δ = 175.5, 168.6, 154.2, 152.2, 148.0, 144.5 (d, J = 10.0 Hz), 138.7, 118.4 (d, J = 8.4 Hz), 110.4 (d, J = 23.6 Hz), 106.0 (d, J = 111.5 Hz), 46.3 (d, J = 4.7 Hz), 43.2, 36.1, 7.5 ppm. HRMS (ESI+) *m/z* calcd for $C_{17}H_{19}FN_3O_3^+$ $[M+H]^+$: 332.1405; found: 332.1421.

See Figure S5 and Figure S6 in the Supporting Information for the XRPD and HPLC analysis, respectively.

Neostigmine methylsulfate (3)

Upstream synthesis of 3: A solution of 3-dimethylaminophenol (**12**) (0.15 M, 1 equiv.) and 18-crown-6 (0.01 M, 0.07 equiv.) in DMF (500 mL) was pumped at a rate of 1.2 mL min^{-1} and combined with a solution of potassium *tert*-butoxide (1 M in THF, 1.3 equiv.) (0.23 mL min^{-1}). After flowing through Reactor I (5 mL reactor) at 40 °C for a residence time of 3.5 min, the resultant stream was mixed with a solution of dimethylcarbamoyl chloride (**13**) (1.5 M in THF, 1.5 equiv.) (0.18 mL min^{-1}) in Reactor II[3b] for 30 s at 40 °C. This stream was then met with an aqueous solution of K_3PO_4 (0.4 M) (2.4 mL min^{-1}) and a stream of toluene (1.6 mL min^{-1}) in a cross mixer to form a triphasic mixture. The mixture was then passed through a membrane separator and the aqueous phase was flowed through a 0.34 MPa BPR and then to waste. The organic stream was next mixed with a stream of deionized water at a T-mixer and passed through another membrane separator, also connected to a 0.34 MPa BPR. This solution was passed through an in-line evaporator at a temperature of 112 °C at a backpressure of 0.41 MPa. Once concentrated (approximately 30% under these conditions), it was mixed with a solution of Me_2SO_4 (5 M in toluene, 3 equiv.) (0.11 mL min^{-1}) and passed through Reactor III (5 mL reactor) at 95 °C, achieving full conversion in 5.5 min and providing the crude neostigmine methylsulfate in 54% yield.

Downstream processing of 3

Precipitation: Ethanol was added to the crude neostigmine methylsulfate suspension obtained from the upstream synthesis (1:2, ethanol:crude) to generate a homogeneous solution, which was then processed in 4 batches offline. Solids were precipitated via the addition of methyl *tert*-butyl ether (MTBE) at a flow rate of 10 mL min^{-1} and a ratio about 50:50, resulting in 38% yield. The solids were then dissolved in ethanol (250 mL) to generate a 39.7 mg mL^{-1} feed solution of neostigmine methylsulfate. This feed solution was processed in the frame through the precipitation tank in 3 batches of 80 mL with 720 mL of MTBE added at a flow rate of 24 mL min^{-1}. Each batch was aged for 20 min prior to pumping into the precipitation unit for filtration. All 3 batches of solids were collected in the precipitation unit before washing with MTBE (200 mL). The slurry was filtered and held under vacuum for 10 min. The solids were dissolved in ethanol (210 mL) under addition for 10 min before pulling the API solution into the crystallization feed tank. The process yield was 82%.

Continuous crystallization: The continuous antisolvent crystallization was carried out using MTBE as the antisolvent at a ratio of solvent:antisolvent of about 10:90. The feed solution and antisolvent were pumped into the first stage CSTR at 0.7 and 4.7 mL min^{-1} respectively. Details of crystallizer volumes and process parameters can be found in the Supporting Information in Table S3. The agitation rate in each stage was 600 rpm. The yield for this process was 85%. Since the resulting solids did not meet purity specifications, the material was processed offline in batch mode following the aforementioned batch precipitation procedure (solids dissolved in ethanol to generate a 40 mg mL^{-1} solution prior to precipitation via the addition of MTBE at a flow rate of 10 mL min^{-1} and a ratio ca. 50:50). The resulting yield was 90%. The slurry was then processed through filtration, washing, and drying steps in frame.

Filtration, washing, drying and formulation: Crystal suspensions were processed in the FWD at 3 mL min^{-1} (25 mL aliquots per 8 min FWD cycle). The filtered material was washed with MTBE:EtOH 90:10 (20 mL) before transfer. Solids were then transferred into the collection chamber and held for 12 h with the heating tape set to 60 °C. Formulation solvent (water) was pumped into the collection chamber with agitation before transferring into the formulation tank. The resulting concentration of the solution was 1.1 mg mL^{-1}. In total, 4.75 g of neostigmine methylsulfate was produced corresponding to 9450 doses (0.5 mg per dose). Given that neostigmine methylsulfate required isolation offline prior to precipitation and a further purification after processing in the downstream unit continuous crystallizers, a production rate cannot be accurately determined. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.80$ (dd, $J =$ 8.5, 2.6 Hz, 1H), 7.63 (t, $J = 2.3$ Hz, 1H), 7.56 (dt, $J = 8.4$, 12.7 Hz, 1H), 7.27 (dd, $J = 8.1$, 1.8 Hz, 1H), 3.75 (s, 9H), 3.67 (s, 3H), 3.11 (s, 3H), 2.98 ppm (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 154.0$, 152.6, 147.7, 131.4, 124.3, 117.0, 114.2, 57.3, 54.5, 36.9, 36.7 ppm. HRMS (ESI+) *m/z* calcd for $C_{12}H_{19}N_2O_2$ $[M]^+$: 223.1441; found: 223.1432. See Figure S9 and Figure S10 in the Supporting Information for the XRPD and HPLC analysis, respectively.

Rufinamide (4)

Upstream synthesis of 4: Streams of 2,6-difluorobenzyl bromide (**14**) (1.0 M in DMSO, 1.0 equiv.) and sodium azide (0.5 M in DMSO, 1.25 equiv.) at flow rates of 1.17 mL min^{-1} and 2.92 mL min^{-1} respectively, were combined and flowed through Reactor I (500 μL reactor, 0.03" id) at ambient temperature for a residence time of 7 s. Neat methyl propiolate (**16**) (1.5 equiv.) (0.16 mL min^{-1}) and ammonia hydroxide (2.25 equiv.) (0.18 mL min^{-1}) were combined and flowed through Reactor II (2 mL reactor, 1/16" id) at ambient temperature for a residence time of 5.9 min. The outcoming streams from Reactors I and II were then mixed with an aqueous solution of sodium ascorbate (3 M, 0.3 equiv.) (0.18 mL min^{-1}). An aqueous solution (0.5 M) of premixed $Cu(OAc)_2(phen)_2$ (phen = 1,10-phenanthroline, 0.05 equiv.) (0.18 mL min^{-1}) was next introduced at a T-mixer using a tube-in-tube reactor and then passed through two static mixers. The final stream was passed through Reactor III (3×10 mL reactors) at 80 °C for a residence time of 6.8 min. A back pressure regulator set at 0.69 MPa was used after the reactor. Steady state was reached after 20 min. Rufinamide was obtained in 77% yield as a solution in DMSO and water.

Downstream processing of 4

Precipitation: The crude rufinamide solution (49.5 mg mL^{-1}) from the upstream synthesis was heated to 50 °C and then processed in the precipitation tank in 3 batches containing 150 mL of the crude and 350 mL of an aqueous solution prepared from ethylenediaminetetraacetic acid (EDTA) (60 mg mL^{-1}) and NaOH (27.3 mg mL^{-1}). Each batch was aged for 20 min before pumping into the precipitation unit for filtration and washing. Solids were washed with water (100 mL) followed by a second wash using water:acetone (50:50, 100 mL). Vacuum was applied for 10 min before dissolving the resulting solids. The washed solid was dissolved in DMSO (175 mL) under agitation for 20 min before pulling the generated API solution into the crystallization feed tank.

Continuous crystallization: The continuous antisolvent crystallization was performed using an aqueous solution prepared from ethylenediaminetetraacetic acid (EDTA) (60 mg mL^{-1}) and NaOH (27.3 mg mL^{-1}). The feed solution and antisolvent (ratio of ca. 30:70) were pumped into the first stage CSTR at 1.3 and 2.6 mL min^{-1} respectively. Details of crystallizer volumes and process parameters can be found in the Supporting Information in

Table S4. The agitation rate in each stage was 600 rpm. The yield for this process was 65%.

Filtration, washing, drying and formulation: Crystal suspensions were processed in the FWD at 1 mL min^{-1} (20 mL aliquots per 20 min FWD cycle). The filtered material was washed with a 50:50 mixture of acetone:water (50 mL). Solids were then transferred into the collection chamber and held for 24 h with the heating tape set to 60 °C. Formulation solvent (50 mL 0.1% poloxamer) was pumped into the collection chamber with agitation before transferring into the formulation tank. The resulting suspension had a concentration of 40.4 mg mL^{-1}. In total 4.75 g of rufinamide was produced corresponding to 20 doses (5 mL of 40 mg mL^{-1} suspension for 1 dose). After start-up and reaching steady state this corresponds to a production rate of 75 doses per day. Given the rufinamide oral suspension has a dose strength (200 mg) over 2 orders of magnitude larger than the oral and ophthalmic dose strengths of neostigmine methylsulfate and ciprofloxacin hydrochloride (0.6 and 0.5 mg, respectively), the doses produced and daily throughput are significantly lower. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.55 (s, 1H), 7.85 (s, 1H), 7.52 (quint, J = 7.5 Hz, 1H), 7.48 (s, 1H), 7.19 (t, J = 8.1 Hz, 2H), 5.72 ppm (s, 2H). ^{13}C NMR (126 MHz, [D$_6$]DMSO) δ = 161.8 (d, J = 7.1 Hz), 161.3, 159.8 (d, J = 7.2 Hz), 142.8, 131.8 (t, J = 10.1 Hz), 126.8, 112.2–111.2 (m), 111.1, 41.2 ppm. HRMS (ESI+) *m/z* calcd for $C_{10}H_8F_2N_4ONa^+$ $[M+Na]^+$: 261.0558; found: 261.0562. See Figure S12 and Figure S13 in the Supporting Information for the XRPD and HPLC analysis, respectively.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: active pharmaceutical ingredients · continuous flow chemistry · industrial chemistry · synthetic methods

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FULL PAPER

Flow Methods

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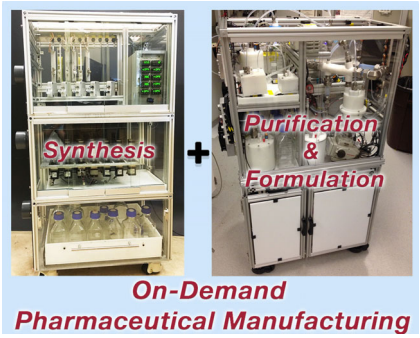
■■ – ■■

Advanced Continuous Flow Platform for On-Demand Pharmaceutical Manufacturing



On-demand pharmaceutical production: The capabilities of a second-generation, compact, continuous flow platform for on-demand pharmaceutical manufacturing are demonstrated with the synthesis of nicardipine hydrochloride and the production of concentrated liquid doses of ciprofloxacin hydrochloride, neostigmine methylsulfate and rufinamide that meet US Pharmacopeia standards.