CASE STUDY

End-to-End ICM Pilot Plant

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INTRODUCTION

Currently, most pharmaceuticals are manufactured via fragmented batch processes, which are time-intensive and expensive. Active pharmaceutical ingredients (APIs) are often produced at one site, and then shipped to a completely different facility for formulation and final transformation into tablets, capsules or other final dosage forms. This inefficient process can require many months, and in some cases more than a year, resulting drug shortages due to these long lead times or quality defects.

The pharmaceutical manufacturing sector is transitioning from batch to continuous operations, seeking the higher efficiencies and improved quality other industries have achieved. For example, semiconductor producers are able to operate six sigma quality processes (~ 0.0003% defects), whereas pharmaceutical manufacturing typically provides 2-3 sigma quality (~ 6.7-30.9% defects; refer to *X. Y. Lawrence and M. Kopcha, Int. J. Pharm., 2017, 528, 354-359*). Thus, this increased interest in continuous manufacturing of APIs and drug products is aligned with the industry's objective of increasing the quality assurance, while enabling rapid production of pharmaceuticals in a significantly reduced footprint, and at a lower cost.

OVERALL PROCESS DESCRIPTION

The current ICM (Integrated Continuous Manufacturing = a novel continuous manufacturing platform where unit operations are run continuously and are integrated to eliminate all the stops-and-starts characteristic of batch processes) process (**Fig. 1**) was developed for a specific generic medication, but it can be modified/reconfigured to produce many other small-molecule pharmaceuticals. It includes the following unit operations: Dissolution & Clarification Bypass, Reactive Crystallization, Filtration, Drying, Extrusion-Molding-Coating (EMC), Solvent Recovery, automated through the Process Control System (DeltaV®) and Process Analytical Technologies (PATs, **Fig. 2**). The process operates at a range of 0.6-2.4 kg/h API, and produces up to 4,800 tablets/h, or 40.3 × 10^6 tablets/year with a total system residence time of < 24 h. Compared with the current batch approach, the ICM process projects a cost reduction of 35-40%, an 80-85% reduction in the number of unit operations (at

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the desired throughput, a single ICM line running on a 24/7 basis is required, whereas multiple batch lines are needed due to heat and mass transfer limitations), a solvent usage reduction of > 55%, a footprint reduction of ~ 90%, and energy savings of 50-60%.

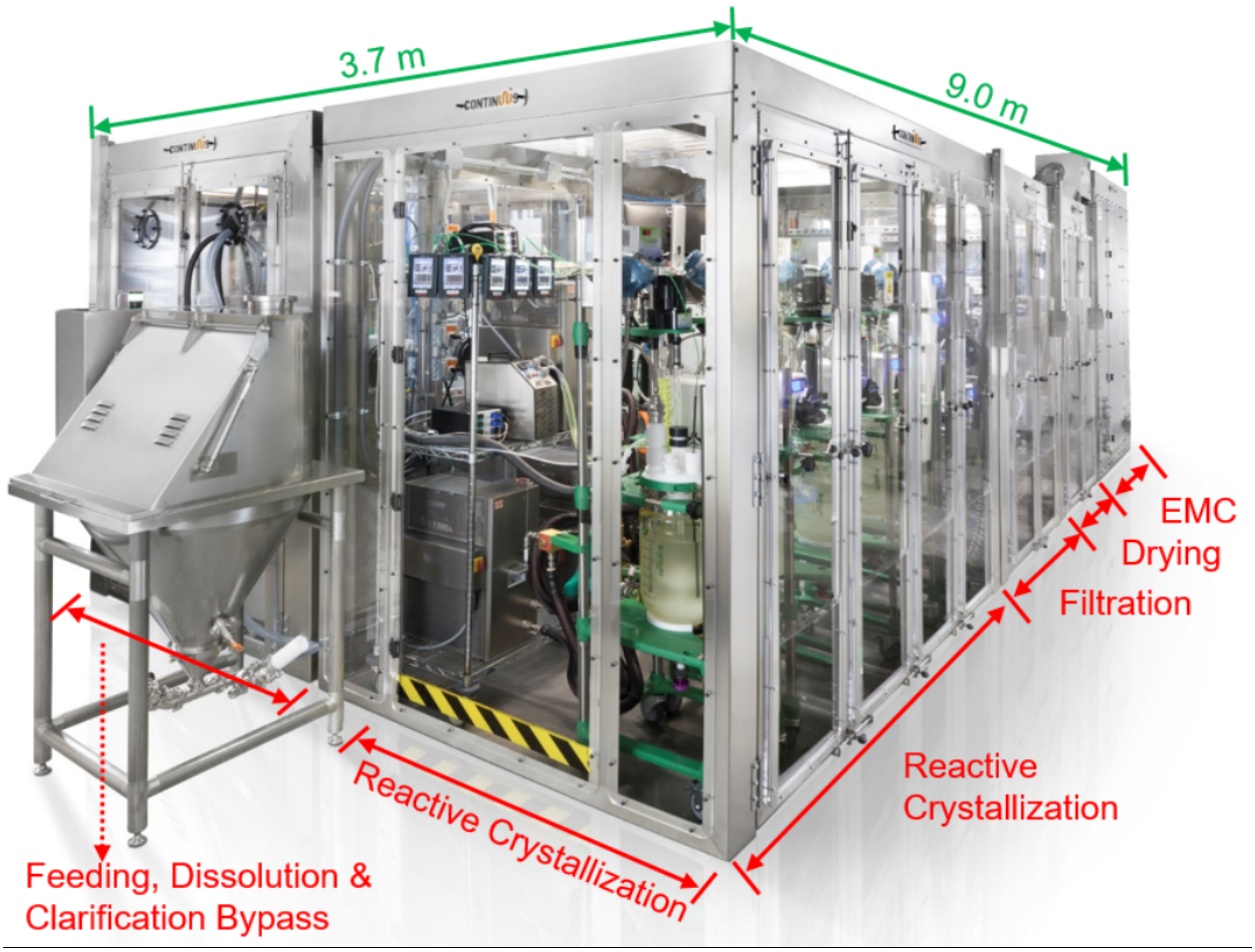

Fig. 1 The ICM pilot plant (with total footprint of 30.7 m2) which includes unit operations of Feeding, Dissolution & Clarification Bypass, Reactive Crystallization, Filtration, Drying, EMC, Solvent Recovery (on the back side), automated through the Process Control System, and Process Analytical Technologies (PATs).

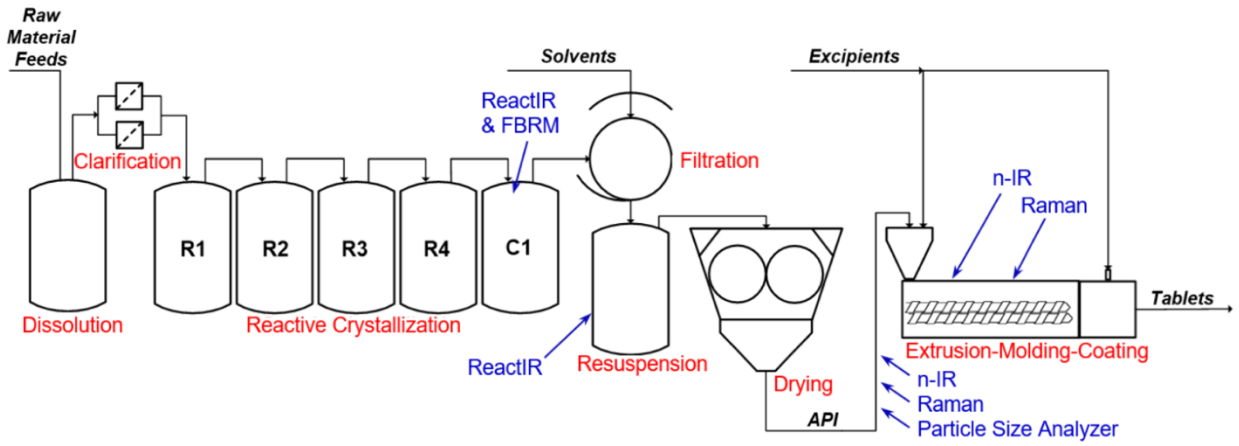

Fig. 2 The ICM process for both API and tablets, and the associated PAT placements (R1-R4: the first to fourth stage reactors; C1: crystallizer).

FEEDING, DISSOLUTION AND CLARIFICATION BYPASS

Raw materials are automatically metered with flowrate control *via* separate feeding systems into the Dissolution Vessel, where the secondary amine hydrochloride (Reactant A) and the nitrile species (Reactant B) are dissolved in Solvent 1 (classified as a dipolar aprotic in the GSK solvent selection guide). Reactants A and B are dispensed with separate feeding systems (**Fig. 3a**), while Solvent 1 is pumped into the Dissolution Vessel. These feed rates to the process are monitored and ratio controlled (Reactant B: Reactant A and Solvent 1: Reactant A) (**Fig. 3b**). In this way, the composition of the pre-reaction mixture is maintained close to the desired values, as verified by offline measurements (**Fig. 3c**). The Dissolution Vessel ensures the complete dissolution of Reactants A and B in Solvent 1. It is a 20 L jacketed vessel equipped with a level sensor, overhead mixer, resistance temperature detector (RTD) probe, and outlet pump. The level (**Fig. 3b**), temperature, and mixer speed are monitored and controlled with the control system. The dissolved un-filtered pre-reaction mixture is fed to the Clarification Bypass system (**Fig. 4**), where suspended particulate matter (SPM) is removed. The Clarification Bypass system consists of two PTFE filter elements (Filters A and B), multiple valves, pressure transducers, and a solvent pump. The control system activates a timed cleaning sequence to clean the filter elements. Fouling is detected by monitoring the pressure difference across the

filter elements (**Fig. 3d**). Offline turbidity measurements are performed before and after filtration to determine if the system is successfully removing the SPM. Prior to passing through the Clarification Bypass system, the solution is turbid (>9.9 Nephelometric Turbidity Units (NTU)), and after filtration the solution is completely clear (0 NTU), indicating the effective removal of SPM.

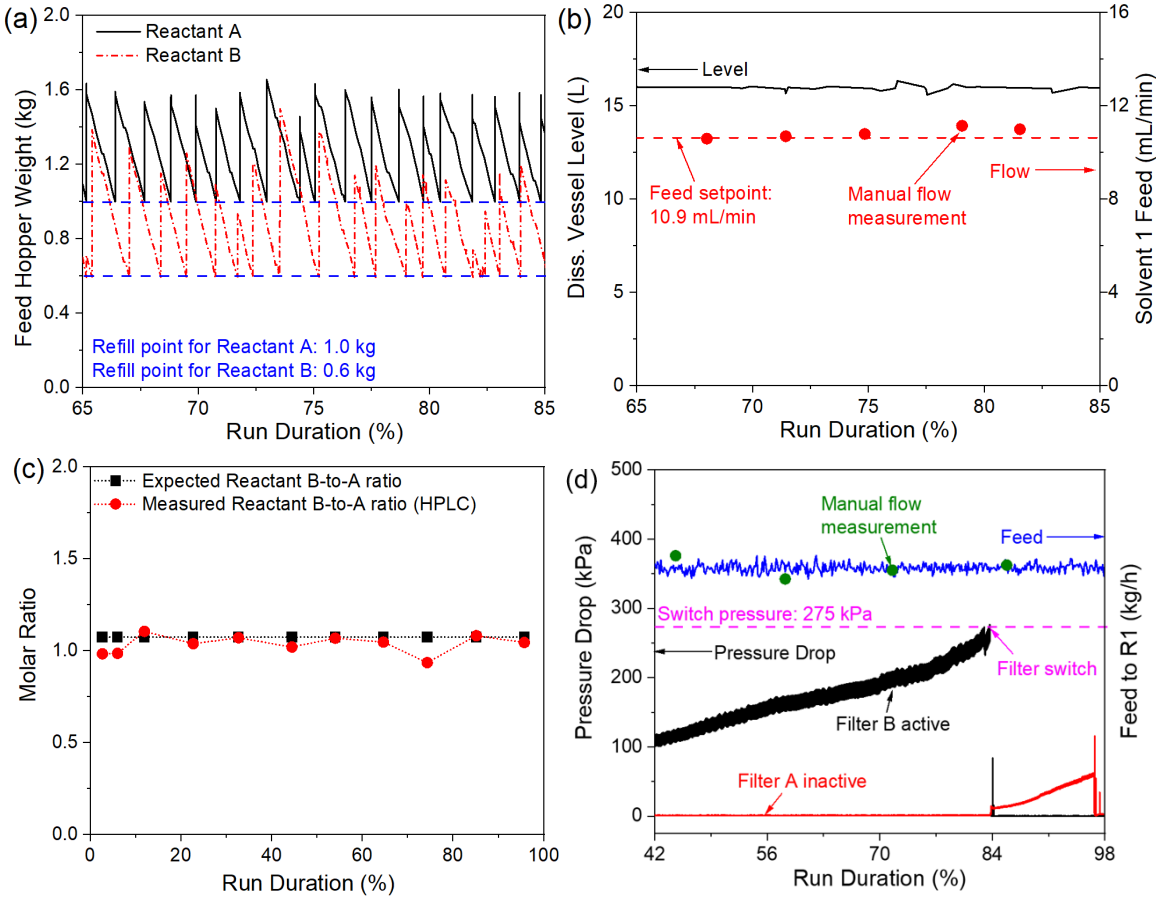

Fig. 3 (a) Reactants A and B feed hopper weights during dispense and refill cycles. **(b)** Dissolution Vessel level under closed loop control with a setpoint of approximately 16 L and the Solvent 1 feed rate setpoint with manual measurements (graduated cylinder). **(c)** Expected and measured Reactant B-to-A molar ratio and **(d)** Pressure drop across both filter elements (A and B).

Fig. 4 Clarification Bypass Unit

REACTIVE CRYSTALLIZATION

The Reactive Crystallization consists of a second order C-N bond-forming reaction between the secondary amine hydrochloride Reactant A and the nitrile species Reactant B. The resulting N,N-dialkyl guanine API adduct crystalizes out as the hydrochloride salt and the process-related impurities remain in the mother liquor. The filtered pre-reaction mixture is pumped into the first stage of the reactive crystallization unit, which consists of five vessels. The first four vessels are reactors (R1-R4, **Fig. 5**), and the last is a crystallizer (C1). All of the vessels are temperature-controlled and equipped with overhead mixers and level sensors.

Fig. 5 Reactive crystallization unit (vessels 1-4)

The levels (**Fig. 6a**) and temperatures (**Fig. 6b**) of each stage can be precisely controlled by changing their setpoints in the control system. The reaction starts in R1 with a reaction yield of 60.6%, which increases to 89.6% in R4 (**Fig. 6c**).

Crystallization also starts in R1 with a crystallization yield of 89.4%, which increases to 98.7% in C1 (**Fig. 6c**). During a 4-day run, the reaction yields and total impurity profiles were very stable in R4 (**Fig. 6d**).

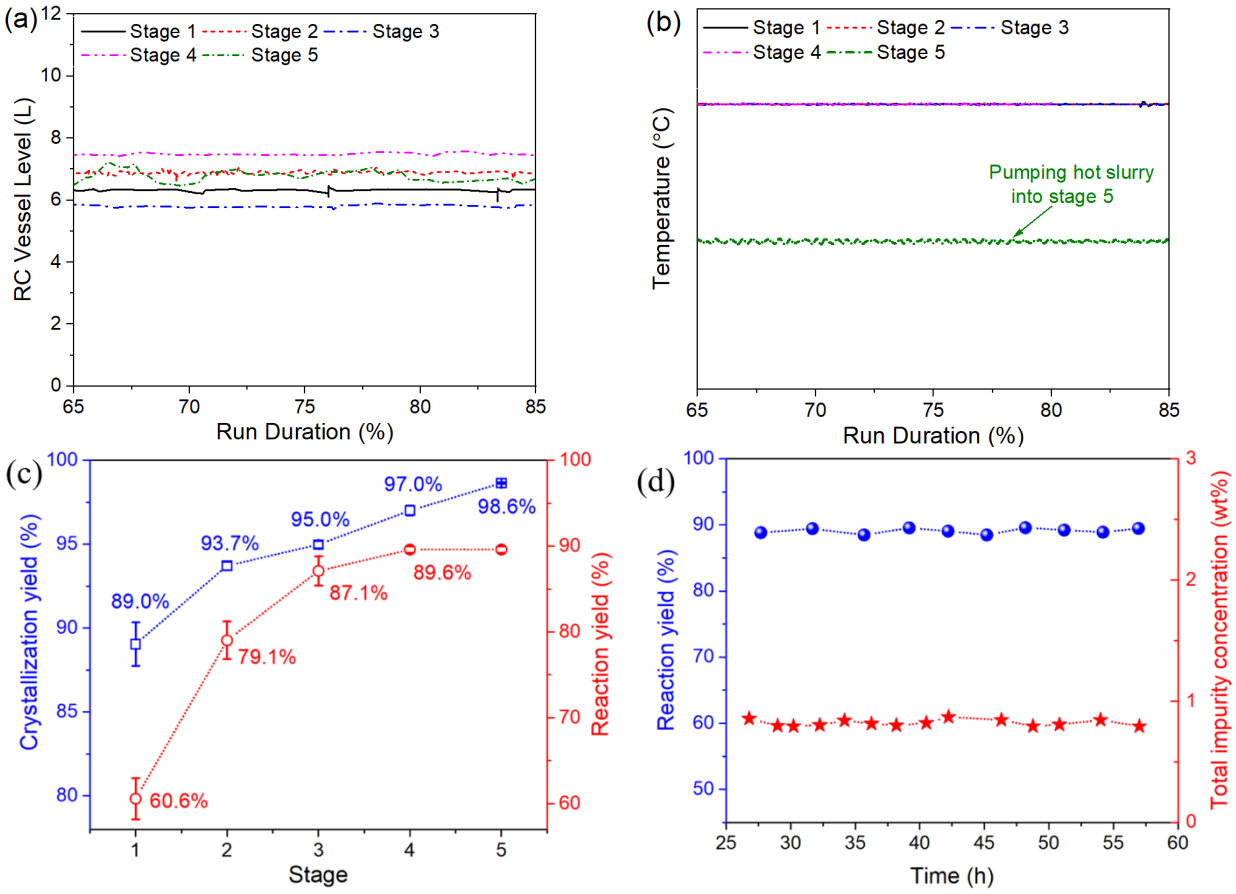

Fig. 6 The five stage Reactive-Crystallization system under closed loop **(a)** level and **(b)** temperature control. **(c)** The reaction and crystallization yields for each stage. **(d)** Reaction yield and total impurity profiles (not including unreacted reactants) during a 4-day run.

FILTRATION

The slurry in the last stage of the Reactive-Crystallization is pumped onto the continuous Rotary Filter (**Fig. 7**) and evenly deposited across the plate through a proprietary automated mechanism, resulting in a wet-cake with a specific height range (*i.e.*, thickness) (**Fig. 8a**). The Rotary Filter separates the API crystals contained in the crude reaction slurry from the mother liquor and purifies the resultant wet-cake. The unit is held under vacuum, and the wet-cake

is washed and purified with pure solvents (Solvent 1 followed by Solvent 2). The purified wet-cake is then transported to a chute through the action of an auger. The slurry feed rate (**Fig. 8a**) and wash flowrate to the filter plate are monitored and controlled, while the vacuum line pressure (**Fig. 8b**) is monitored.

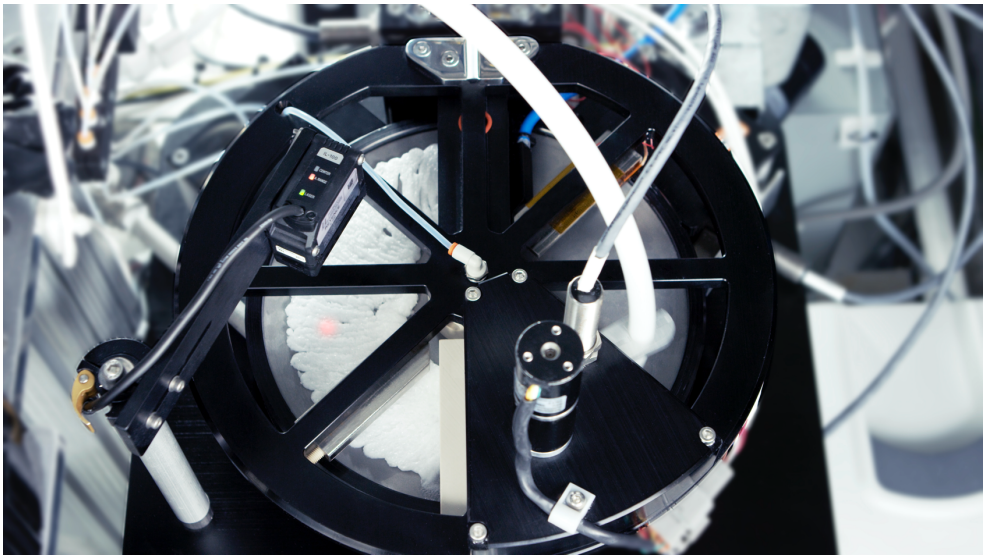

Fig. 7 CONTINUUS Rotary Filter

The Solvent 1 cake wash feed rate influences the resultant purity of the wet-cake. The temperature in the last stage of the Reactive-Crystallization system also impacts purification performance. At lower temperatures (T1) purification performance decreases, whereas at higher temperatures (T2) purification performance increases, despite the same reaction and cake wash conditions (**Fig. 8c**). After purification, the wet-cake is re-suspended in Solvent 2. The Resuspension Unit is equipped with a level sensor, an overhead high-shear mixer, a ReactIR 15 system, a FBRM probe, and an outlet pump. It is level controlled and a precise solids weight loading (wt%) is maintained at a desired setpoint (**Fig. 8d**) with a Solvent 2 dilution stream. Purity of the re-suspended slurry, on a dry mass basis, is assessed prior to feeding the slurry to the Drum Dryer. Stable impurity profiles (within specification) in the Resuspension Unit were observed during the run.

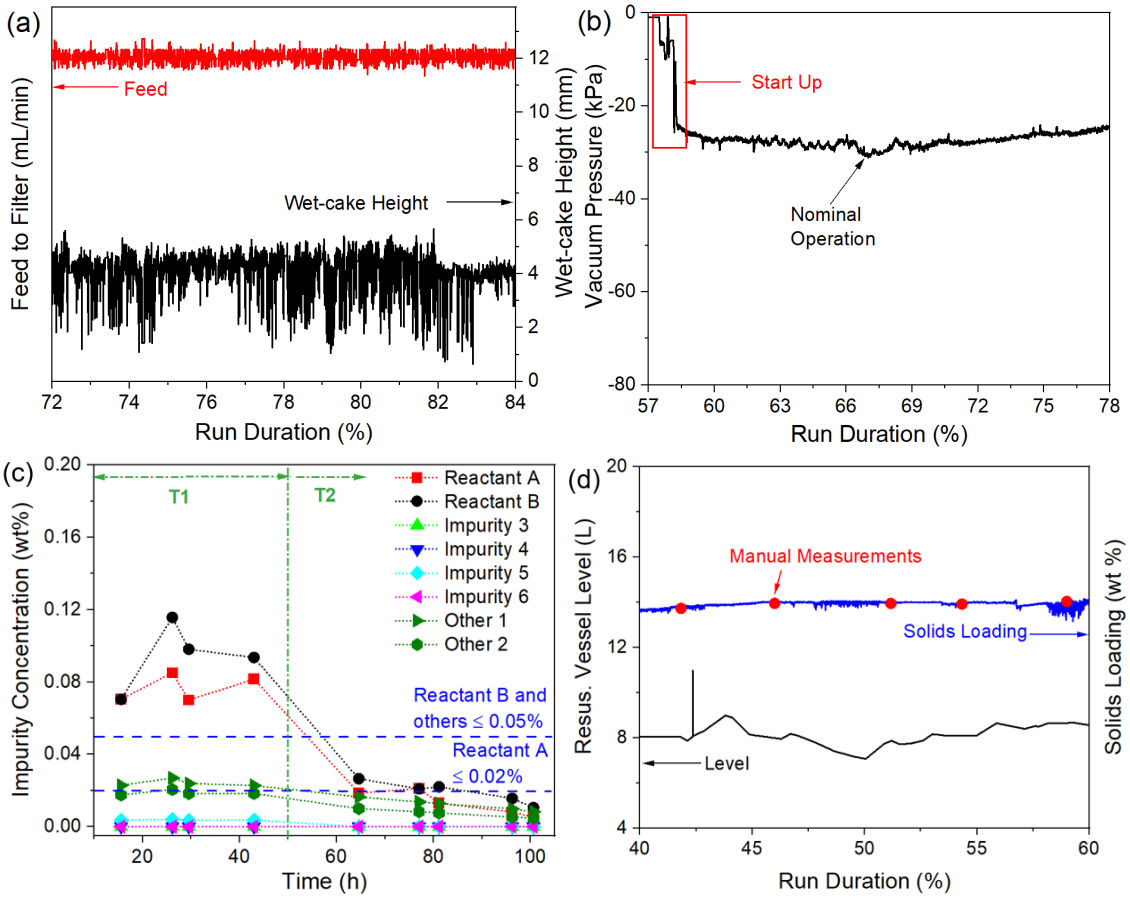

Fig. 8 (a) Stable slurry feed from the 5th Stage of the Reactive-Crystallization and wet-cake height (i.e., thickness). **(b)** Vacuum pressure on a filter plate during start-up and nominal operation. **(c)** At lower temperatures (T1) the impurities are more difficult to remove than at higher temperatures (T2) at the same Reactive-Crystallization and wet-cake solvent wash rate conditions. **(d)** Resuspension Vessel level and solids weight loading (with manual measurements) in closed loop control.

DRYING

Slurry is fed from the Resuspension Unit into the Drum Dryer (**Fig. 9**) at a constant rate (**Fig. 10a**). The Drum Dryer is used to evaporate solvent and further reduce the particle size of the crystals in the feed slurry. The continuous Drum Dryer consists of two heated, rotating drums, and is held under vacuum. The drum temperatures (**Fig. 10a**), gap load force between the drums, vacuum pressure (**Fig. 10b**), and gas exhaust flowrate (**Fig. 10b**) are monitored and controlled with the control system. The material is dried on the heated surfaces of the drums as they rotate. On the lateral positions of each drum are scraper blades that completely remove the material from the drum surfaces, leaving no residual material. The dried API falls down a chute as a flowing powder, and is

fed to a cyclone separator. The cyclone separates the evaporated solvent from the API, which drops into an airlock system.

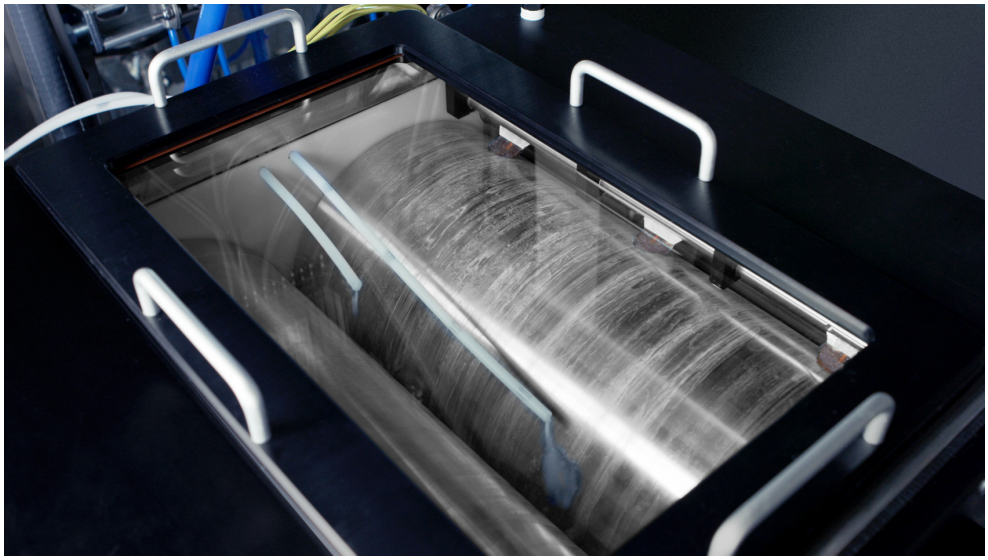

Fig. 9 CONTINUUS Drum Dryer

The system is designed to keep the drum chamber under vacuum, while concurrently allowing the API to exit at atmospheric pressure and be conveyed to the EMC machine. API within the residual solvent specifications for both Solvent 1 and 2 is produced (**Fig. 10c**). PSD is also an important quality attribute for the API, as it can affect the dissolution of the tablets. As previously noted, a high-shear mixer is located in the Resuspension Unit, which reduces the particle size of the wet-cake crystals. Additionally, the drum gap force applied between the drums further reduces the particle size. **Fig. 10d** shows the particle size reduction from wet-cake, to re-suspended slurry, to API.

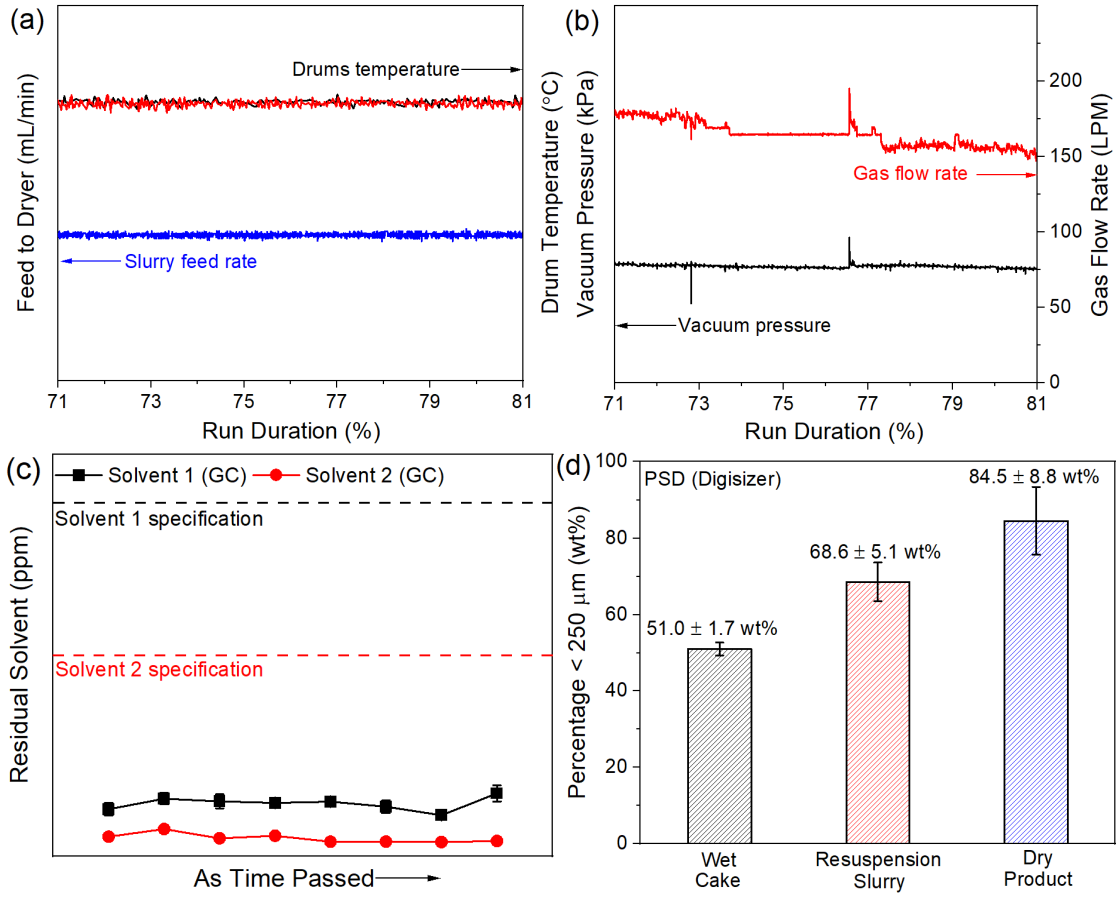

Fig. 10 (a) Slurry feed rate to dryer and drum temperatures of left and right drums. **(b)** Vacuum pressure and gas flowrate during nominal operation. **(c)** Residual solvent contents in the API relative to their specifications. **(d)** Particle size profile from wet-cake, to re-suspension slurry, to dry product.

EXTRUSION-MOLDING-COATING (EMC)

The API from the Drum Dryer and a polymer blend are simultaneously fed into the EMC machine (**Fig. 11**) in a 50:50 mass ratio (**Fig. 12a**) with separate feeding systems. The EMC machine is a combined Twin Screw (TS) Hot Melt Extrusion (HME) and injection molding system that is capable of producing coated tablets. The extruder section has multiple temperature-controlled zones (**Fig. 12b**), and also serves to process (heat, mix, and shear) the polymer melt. The extrusion operation has many variables that are monitored and controlled, such as torque on the twin screws (**Fig. 12a**). From the extruder, the material passes through a transfer manifold (transition point between the extruder and core injection unit) to the core injection barrel. The temperature-controlled core injection unit injects material, under pressure, into the mold for tablet core formation.

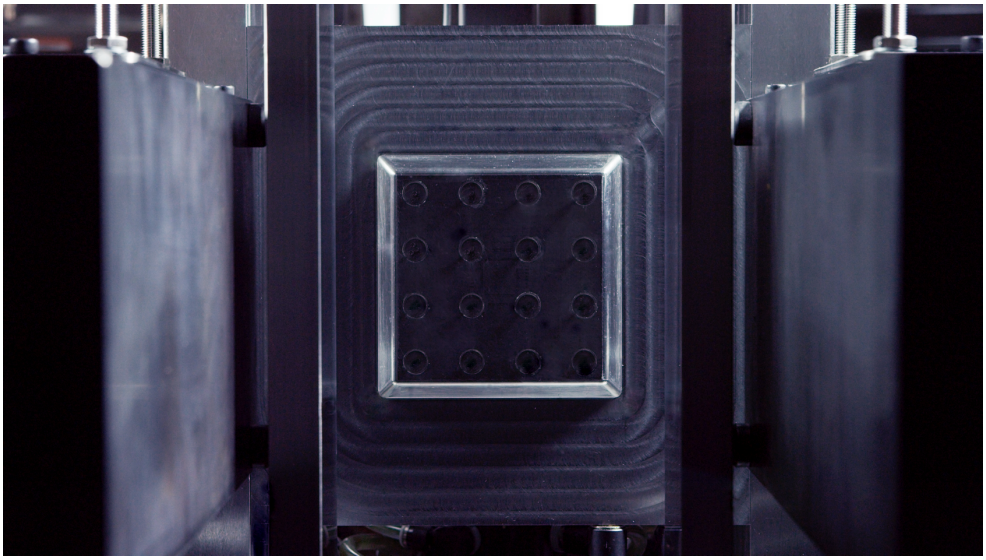

Fig. 11 EMC Machine (tablet mold detail)

The API retains its crystalline state and is homogenously dispersed (as crystals) in the polymeric matrix. Stability is ensured, as the crystalline state is the most thermodynamically stable state. Depending on the formulation, a coating can be applied. The tablets (**Fig. 13a**) are tested for API assay (**Fig. 13b**), dissolution (**Fig. 13c-d**), and impurities (**Fig. 13d**) offline. All associated specifications were met and confirmed by multiple tests. The extrudate is analyzed with n-IR and Raman spectroscopy in the transfer manifold for content uniformity and crystallinity/form, respectively.

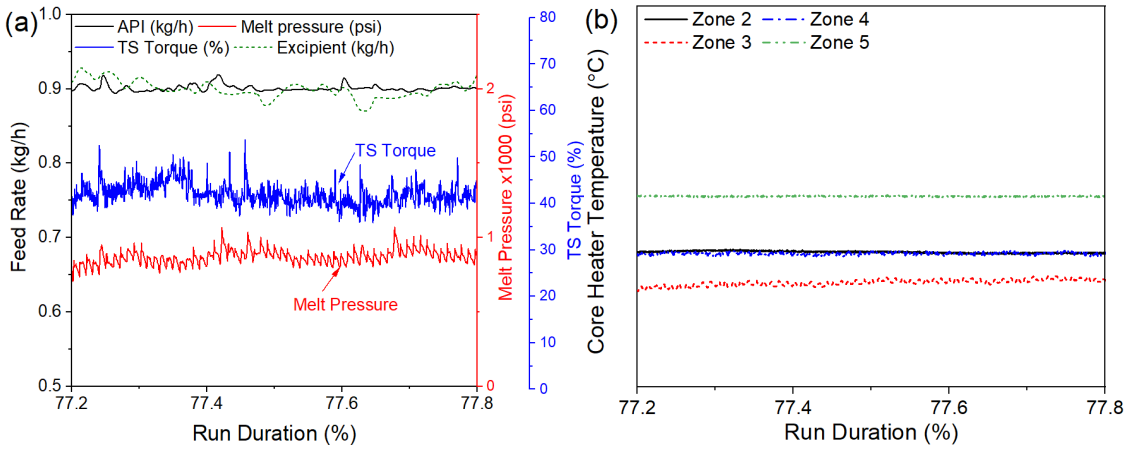

Fig. 12 (a) Feed rates (50:50 mass ratio) of the API and polymer blend to the EMC, including important process parameters (torque and melt pressure). **(b)** Temperature profiles in the mold of the machine.

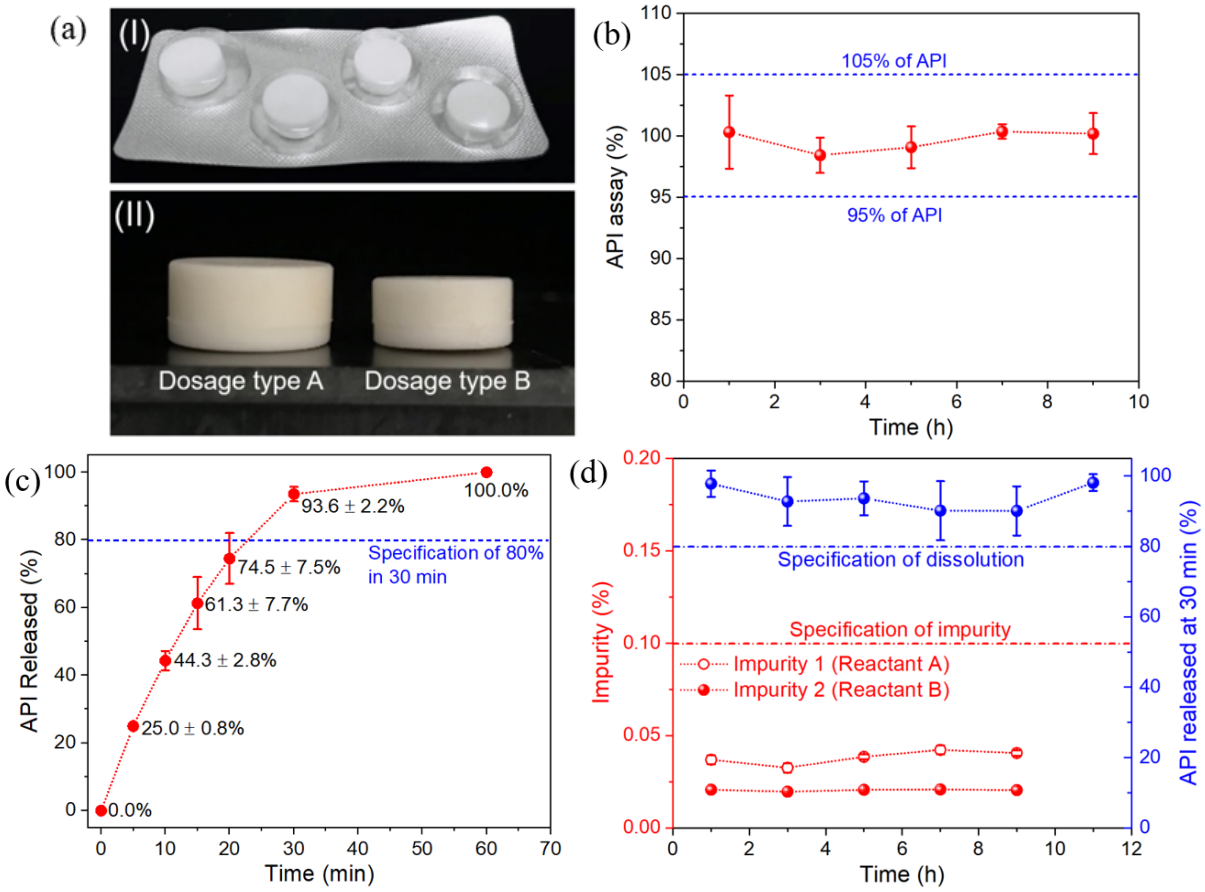

Fig. 13 (a) (I) tablets in the primary packaging, and **(II)** comparison of different dosage tablets. The current formulation has no coating, however, the EMC unit is capable of coating the tablets. **(b)** API assay of the tablets. **(c-d)** Dissolution tests and impurity profile of the tablets.

PLANT-WIDE CONTROL

A DeltaV plant-wide control system from EMERSON is used for monitoring, controlling, and recording process variables. A configure-to-order (CTO) control cabinet is equipped with input/output (I/O) cards that facilitate measurement acquisition (e.g., temperature, pressure, force) and equipment control (e.g., pumps, valves, motors). Servers are used to compute and store data and connect to Ethernet cables that communicate with certain equipment (e.g., PAT computers). Operators monitor and control the process through a graphical user interface (GUI). The process control system is an essential component of the ICM pilot plant, and serves to mitigate process disturbances while maintaining the system in a state of control. During the ICM process, an active control strategy ensures product quality by real-time adjustment of the process parameters. **Fig. 14a-b** show the real-time control algorithm of feeding reactants and solvent to

maintain a stable Reactant B-to-A ratio, which ensures the successful completion of the reaction.

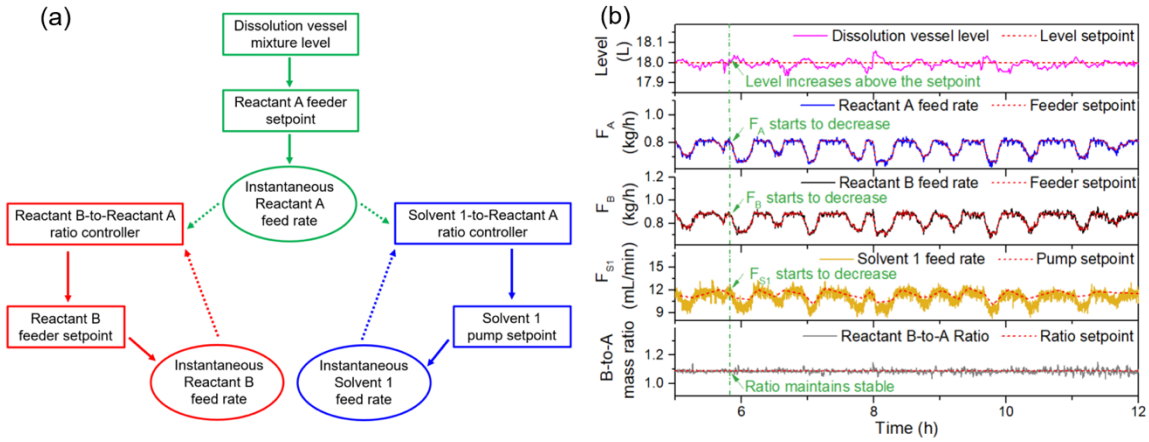

Fig. 14 An example demonstrating the active control strategy. **(a-b)** The real-time control algorithm for feeding Reactants A and B, and Solvent 1 provides a stable Reactant B-to-A ratio (FA: feed rate of Reactant A; FB: feed rate of Reactant B; FS1: feed rate of Solvent 1).

TRACK OF CRITICAL MATERIAL ATTRIBUTES (CMAS)

The CMAs across the entire process are tracked by the appropriate PATs (**Fig. 15**), which are key components of the ICM pilot plant that enable the monitoring and control the process. Examples of PATs and their respective CMAs include: ReactIR (for Reactant concentration), n-IR (for residual solvent), Digisizer (for particle size distribution) and more)

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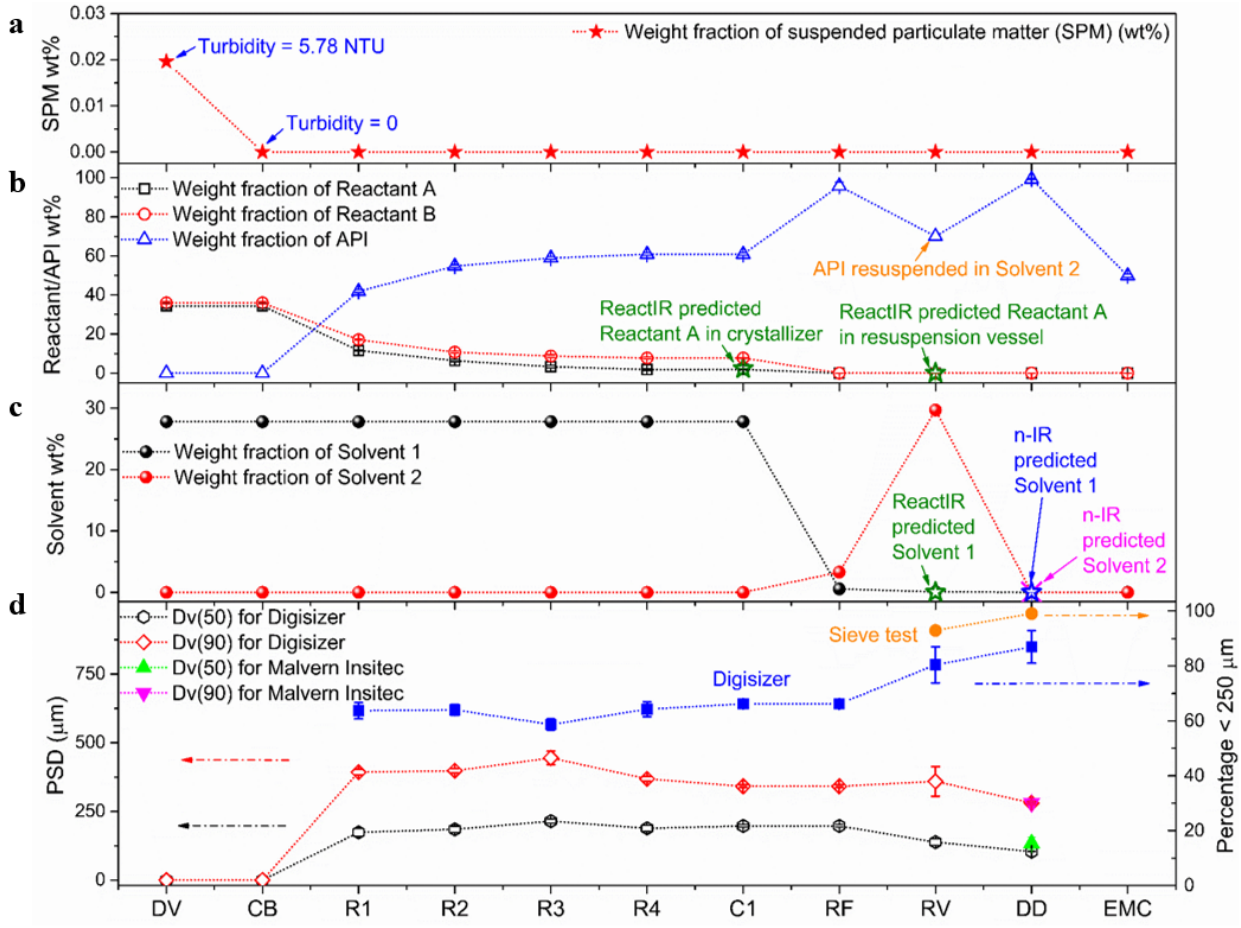

Fig. 15 Tracking of the CMAs across the ICM process. **(a)** SPM weight fraction. **(b)** Reactants and API weight **fractions. (c)** Solvents 1 and 2 weight fractions. **(d)** Particle Size Distribution (PSD)/Chord Length Distribution (CLD) of the API crystals. (DV=Dissolution Vessel; CB=Clarification Bypass; R=Reactor; C=Crystallizer; RF=Rotary Filtration; RV=Resuspension Vessel; DD=Drum Drying; EMC=Extrusion-Molding-Coating). Dv (50) and Dv (90) are the particle sizes at the 50th and 90th percentiles of the cumulative size distribution respectively.

For detailed information, please refer to our publication: (1) Design and Commercialization of an End-to-End Continuous Pharmaceutical Production Process: A Pilot Plant Case Study. Org. Process Res. Dev. 2020, 24, 12, 2874-2889; (2) An automated modular assembly line for drugs in a miniaturized plant. Chem. Commun., 2020, 56, 1026-1029.