Supplementary Materials for

An automated modular assembly line for drugs in a miniaturized box

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Captions for Movies S1

End-to end integrated continuous manufacturing (ICM) process with a modular design.

Process Details

PAT

As shown in Fig. 1c, a ReactIR 15 system and FBRM from Mettler Toledo are used to monitor in real-time Reactant A concentration (by monitoring the scissoring of the –NH2 groups) and the chord length distribution (CLD) of the crystals in the crystallizer (C1), respectively. The ReactIR 15 system is also located in the resuspension vessel to monitor the concentrations of Reactant A and Solvent 1. An n-IR probe is implemented after the drum dryer, specifically to measure the residual content of Solvents 1 and 2. A second n-IR probe is located in the extruder unit of the EMC, to monitor the content uniformity of API in the polymer melt. Two RamanRxn2 probes from Kaiser Optical System Inc. are located post-drum dryer, and within the extruder, respectively, to monitor crystal form. An Insitec system from Malvern is implemented post-drum dryer, to measure the particle size distribution (PSD) of the dried API.

Dissolution & Clarification Bypass

Turbidity is a measure of the degree to which liquid loses its transparency (in this case due to the presence of SPM). The greater the amount of SPM, the murkier the solution appears. Fig. S1 shows the turbidity measurements of the unfiltered and filtered pre-reaction mixture during a 4-day run. After the Clarification Bypass, the turbidity decreased to zero, indicating the effective removal of the SPM.

Reactive Crystallization

The reaction starts in R1 with a reaction yield of 60.6%, which increases to 89.6% in R4 (Fig. S2a). Crystallization also starts in R1 with a crystallization yield of 89.0%, which increases to 98.6% in C1 (Fig. S2a). ReactIR is a mid-infrared based system that provides real-time, in situ information about the reaction progress. Fig. S2b shows a good match between the ReactIR predictions of the Reactant A concentration in C1 (taken at different time points during the run), and their corresponding HPLC results (percent error < 0.17%). An FBRM is inserted into C1 to track CLD in real-time. The mean square-weighted chord lengths of the crystals ranged from ~ 143-156 μm (Fig. S2c). The CLD can be fine-tuned by changing several operating parameter setpoints (e.g., temperature, mixing rate, residence time) in the control system.

Rotary Filtration

At steady state, the vacuum pressure is approximately between -30 and -24 kPa, and the wet-cake height is ~ 4 mm (Fig. S3). To meet the final particle size specification, a high-shear mixer could be used in the resuspension vessel to reduce the particle size (Fig. S4a).

Drum Drying

The compression force of the drum drier, coupled with the high-shear mixer action, allows for effective PSD control of the final dried API. Fig. S4b shows a good match of PSD measurements between the in-line Malvern Insitec and off-line Digisizer measurements.

Extrusion-Molding-Coating (EMC)

Compared to powder compression, the EMC system provides better mixing between the API and excipients and a higher degree of content uniformity (Fig. S5). However, different factors (e.g., thermostability of the API, thermoplasticity of the main polymer excipient, viscosity of the formulation) need to be considered for formulation development.

Solvent Recovery

Solvent Recovery is a supporting unit for the ICM process, which greatly reduces the solvent usage and therefore operating cost. Fig. S7a provides the recovery yield and purity of the recovered solvents. After integrating Solvent Recovery, the E-factor (defined as the mass of the total waste generated relative to the mass of the desired product formed) (*R. A .Sheldon, Chem. Commun., 2008, 3352-3365*) decreased from 0.77 to 0.21 for the current ICM process (Fig. S7b). To form the same number of tablets, a corresponding batch process generates ~ 30% more waste than the end-to-end ICM process described. Thus, the ICM process allows for a more environmentally sustainable manufacturing system for the pharmaceutical industry.

Supporting Figures

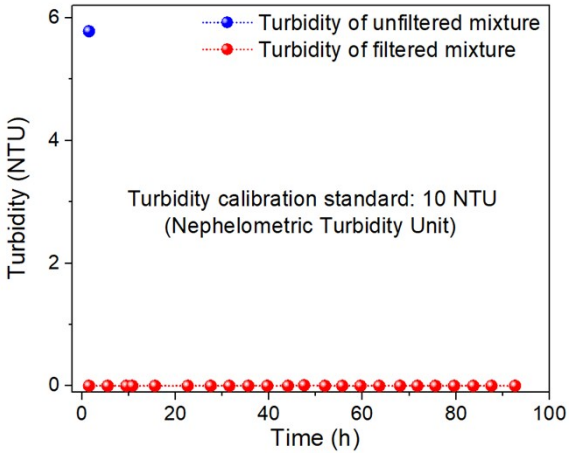

Fig. S1 Turbidity measurements of unfiltered (blue) and filtered (red) pre-reaction mixture.

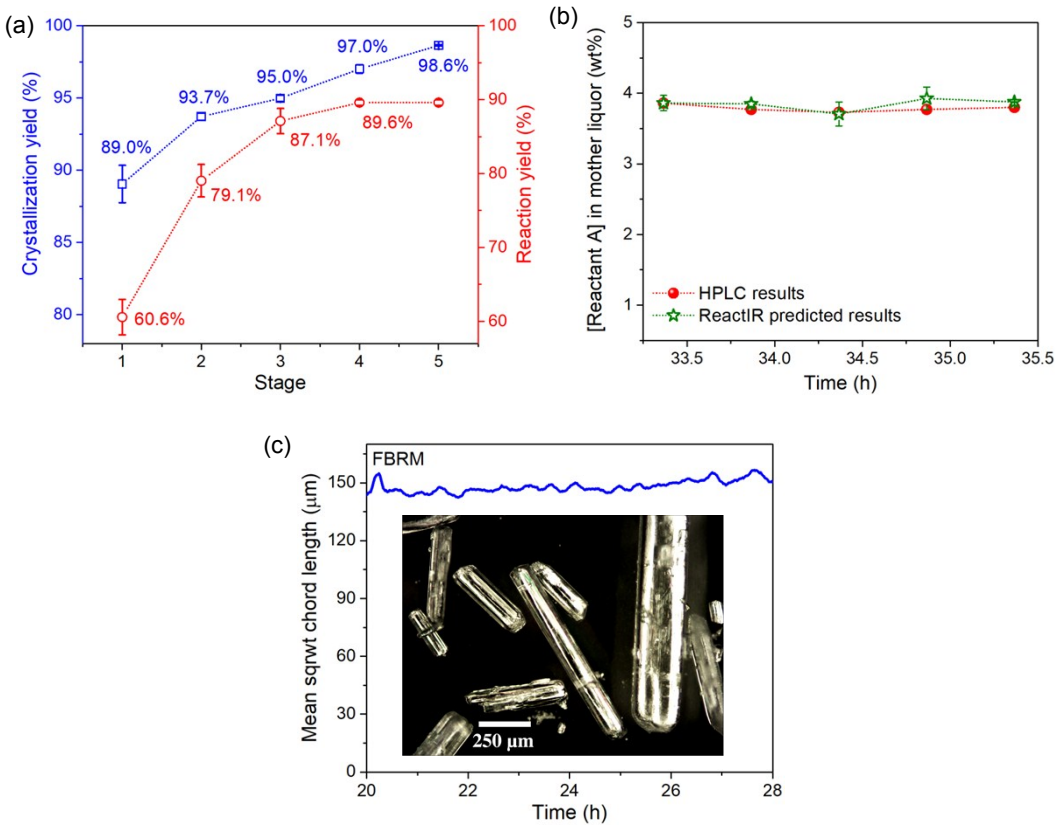

Fig. S2 (a) Reaction and crystallization yields in R1-C1. (b) ReactIR predicted Reactant A compared to HPLC results. (c) The in-line FBRM data and a microscope image of the particles in C1.

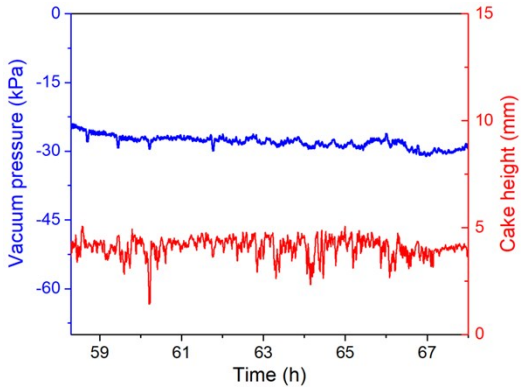

Fig. S3 The vacuum pressure and wet-cake height in the filter at steady state condition.

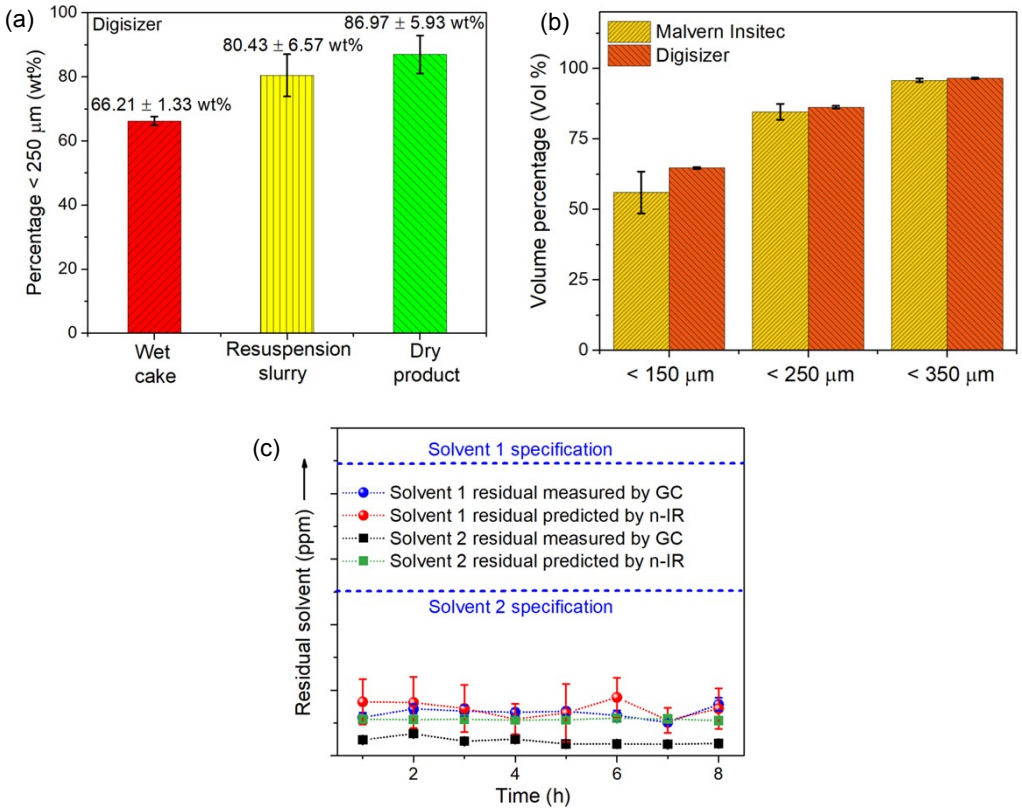

Fig. S4 (a) PSD measurements for wet-cake, resuspension slurry, and dry API. (b) Microscope image of the dry API. (c) The dry API meets the residual solvents specifications. Both solvent specifications are below 1000 ppm.

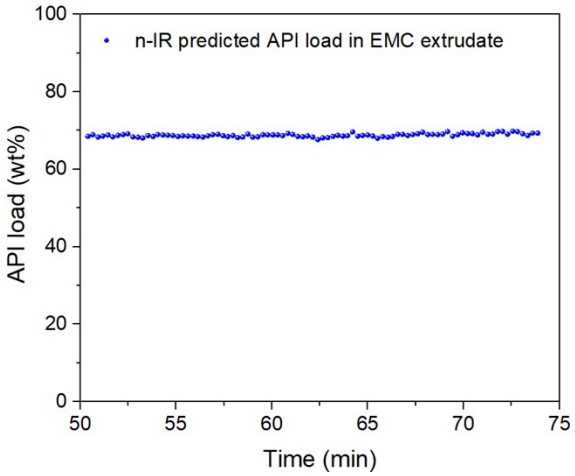

Fig. S5 The n-IR predicted API load in the EMC extrudate

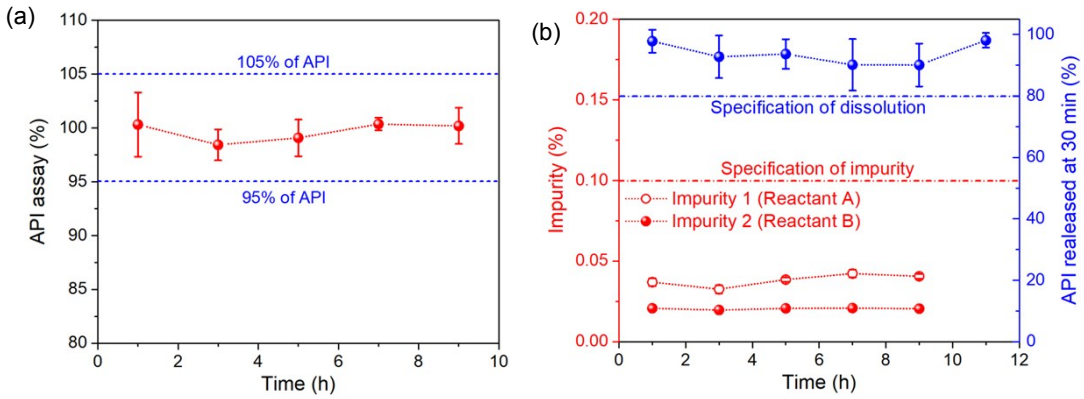

Fig. S6 (a) API assay of the tablets. (b) Impurity profile and dissolution test of the tablets.

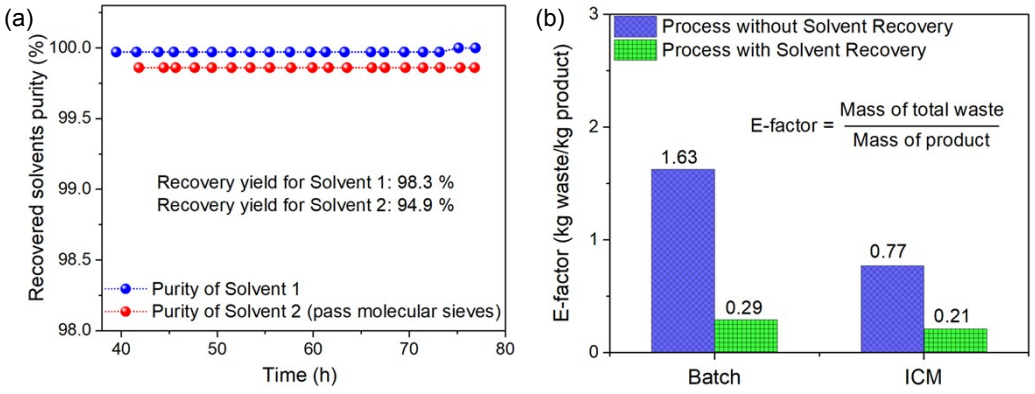

Fig. S7 (a) Purity and recovery yield of the recovered Solvent 1 and Solvent 2. (b) E-factor analysis of the batch and ICM processes with and without Solvent Recovery.