Continuous Flow Droplet-Based Crystallization Platform for Producing Spherical Drug Microparticles

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ABSTRACT: In this paper, we demonstrate a continuous flow evaporative crystallization platform for producing monodisperse microparticles containing crystalline API with tunable particle sizes and compositions, which are suitable for direct compounding. Monodisperse drug-laden emulsions are first generated via microfluidics and undergo continuous solvent extraction within a tubular crystallizer to emerge as microparticles. We demonstrate this platform on four different types of hydrophobic drug and drug-excipient formulations to show the generality of this method and discuss the solvent extraction performance of the platform using a mathematical model. Our approach combines four conventional manufacturing steps in the conventional secondary drug manufacturing cycle—crystallization, blending, milling, and granulation, into a single step which directly produces monodisperse and spherical microparticles of tailored size and composition. This system paves the way for innovative continuous bottom-up formulation of microparticles and is aligned with the expanding suite of advanced continuous pharmaceutical manufacturing technologies.

KEYWORDS: pharmaceutical crystallization, drug product formulation, advanced continuous manufacturing, particle technology, emulsion-based crystallization

1. INTRODUCTION

There is a paradigm shift in pharmaceutical manufacturing, away from traditional batch manufacturing, toward agile and modular continuous processing methods for both chemical synthesis and drug product formulation.1–4 While flow chemistry has been well used and demonstrated for active pharmaceutical ingredients (API) synthesis in both research and industrial contexts over the past decade,5,6 there is a conspicuous demand for advanced continuous processes for drug product formulation,7,8 which includes operations such as crystallization, milling, sieving, blending, roller compaction, and tableting.

To this end, several groups have made significant improvements to crystallization processes utilizing continuous mixed

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spherical microparticles to be formed. Our platform is an evolution of our previously demonstrated semibatch microfluidics-based technique, in which we are able to form monodisperse drug or drug composite particles in a wide range of tunable sizes. This one-step coformulation of drugs and excipients into monodisperse composite microparticles ensures homogeneity of particle compositions across the particle population, eliminating the need for subsequent milling and blending. When coupled with large scale liters-per-day emulsion generators, this platform offers the potential ability to proceed with kilo-scale continuous droplet processing (via online evaporative crystallization) for feasible manufacture of spherical drug or drug-excipient microparticles. This process is highly versatile, and emulsion solvent systems may be selected to cater to different types of drugs (hydrophilic or hydrophobic). Here, we demonstrate this using dichloromethane in water droplets with four different types of hydrophobic drugs and drug-excipient formulations: GSK1 (a hydrophobic GSK asset), GSK1-ethyl cellulose, indomethacin-ethyl cellulose, and 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophene-carbonitrile (ROY)-poly(lactic-co-glycolic acid) (PLGA). To characterize the removal of dichloromethane from the droplets in the system, we also present a simple mathematical model for predicting dynamic droplet size change. The particles generated from this platform enable the creation of drug product intermediates, which may bridge the traditional gap between primary and secondary drug manufacturing processes. This versatile platform is thus a demonstration of process intensified advanced continuous formulation methods which can be directly implemented and integrated with upstream continuous flow synthesis units.

2. EXPERIMENTAL SECTION

Materials. Poly(vinyl) alcohol (PVA) (M.W. 67 000), dichloromethane (99.5%), Glycerol, Ethyl cellulose (EC) (viscosity 10 cP), Poly(lactic-co-glycolic acid) (PLGA) (50:50), and Indomethacin (IND) were purchased from Sigma-Aldrich (Singapore) and used as received. 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophene-carbonitrile (ROY)-poly(lactic-co-glycolic acid) (PLGA). To characterize the removal of dichloromethane from the droplets in the system, we also present a simple mathematical model for predicting dynamic droplet size change. The particles generated from this platform enable the creation of drug product intermediates, which may bridge the traditional gap between primary and secondary drug manufacturing processes. This versatile platform is thus a demonstration of process intensified advanced continuous formulation methods which can be directly implemented and integrated with upstream continuous flow synthesis units.

Methods. (i) Emulsion generation: A MicroTee of 0.150 mm I.D. (P-890, 1/16”, WO 864844) was utilized for the generation of dichloromethane-in-water droplets containing the drug/drug-excipient mixture. An aqueous solution of 10 wt % glycerol and 3 wt % PVA was prepared as the continuous phase (W), while the dispersed phase was a dichloromethane or dichloromethane-methanol solution containing the dissolved drug or drug-excipient mixture. The compositions of the dispersed phase (O) used for formulation were as follows: 16 mg/mL of GSK1 in a dichloromethane-methanol (80:20 vol %) cosolvent mixture, 16 mg/mL of GSK1 and 5 mg/mL of ethyl cellulose in a dichloromethane-methanol (80:20 vol %) cosolvent mixture, 50 mg/mL of indomethacin and 50 mg/mL of ethyl cellulose in dichloromethane, and 240 mg/mL of ROY and 40 mg/mL of PLGA (50:50) in dichloromethane. Cosolvent mixtures were employed to increase the solubility of the drug and excipient. W and O phases were infused into the MicroTee using syringe pumps (Harvard PHD 22/2000), at flow rates of 500–600 μL/min and 100 μL/min respectively in order to keep the emulsion sizes within 400–500 μm. An additional stream containing the continuous phase was added downstream of the emulsion generation device using a Y-connector, at flow rates of 100–700 μL/min. The inlet tubes for the continuous and dispersed phases were 1.0 mm and 0.254 mm I.D. PTFE tubes, respectively. A 5 cm PEEK tube with a 0.1778 mm I.D. was also attached to the end of the 1.0 mm I.D. continuous phase inlet PTFE tube just before the MicroTee to prevent any backflow of emulsions into the tube during operation. Lastly, a 0.5 mm I.D. FEP tube was used as the outlet tube for the MicroTee leading to the silicone tube of the perstraction unit.

(ii) Solvent removal: A 4 mm silicone tube with a 0.8 mm I.D. was chosen as the perstraction tube for solvent extraction. The tube walls are wet by the continuous aqueous phase, while the emulsions flow along the tube length in a laminar flow regime. The entire tube was immersed in an open water bath (~700 mL) maintained at 48 °C, with stirring set at 350 rpm. Upon passing through the tube, the emulsions shrink to a certain extent before exiting the tubes to enter the glass condenser, depending on their flow rates and initial droplet diameters. Measured residence times for flow rates of 700–1300 μL/min are 3–5 min.

(iii) Solidification of microparticles: A graham type glass condenser of 600 mm effective length, 6 mm I.D. inner coil, 30 coils (1.5 m in inner coil length) was chosen as the vessel for final extraction of solvent from the microparticles. To implement a stratified, bilayer gas–liquid flow in the glass coil, inert nitrogen gas at near atmospheric pressure (115 kPa, ~50 cm3/s) was introduced at the top of the condenser along with the inlet of the aqueous stream containing the emulsions. An additional aqueous ultrapure water stream flowing at 600–1800 μL/min was also introduced at the top of the graham condenser, to dilute the outgoing stream from the perstraction unit and increase the physical spacing between adjacent droplets within the condenser. The measured residence time of the aqueous stream in the condenser was 1.5 min. A stratified gas–liquid two-phase flow was effectively formed within the inner coil of the condenser, with the gas atop the aqueous stream containing the emulsions. A peristaltic pump (Leadfluid BT-50S, YZ-1S) was used to circulate silicone oil, as the heating fluid in the shell of the condenser, and was added at the bottom of the condenser in a counter current configuration at a temperature of 80 °C. The temperature of the silicone oil was verified using an FLIR ONE thermal imaging camera mounted on an iPhone 5s. The microparticles collected at the outlet of the condenser were washed with ultrapure water and vacuum-dried immediately before further characterization.

(iv) Droplet shrinkage trends: A series of flow studies were conducted to validate a mathematical model of droplet
shrinkage across the perstraction unit. Silicone tubes with the same inner diameter of 0.8 mm but varying tube wall thickness of 0.8 mm and 1.6 mm were used to conduct perstraction at the same flow conditions. A high speed digital camera (Basler pI640) was mounted on a stereomicroscope (Leica MZ16) to capture the droplet sizes at 0, 2, and 4 m of the tubes for subsequent size measurements, and the flow rates of the dispersed phase and continuous phase were varied to tune the residence time of the droplets; three sets of independent droplet shrinkage data were obtained for the two tubes at identical flow conditions ($F = 6, 8, 12$, where $F$ is the volumetric ratio of water and dichloromethane introduced into the silicone tube membrane) and initial droplet diameters (450 μm).

Characterization. Optical microscopy images of the process and samples were captured using a QImaging MicroPublisher 5.0 RTV camera mounted on an Olympus SZX7 microscope. A Leica CLS 150 XE light source was used for illumination. A field emission scanning electron microscope (JEOL JSM-6700F) at 5 kV accelerating voltage was used to acquire further structural information on the microparticles. All samples were prepared on conventional SEM stubs with carbon tape and were coated with ~10 nm of platinum by sputter coating. To reveal the cross sections of the microparticles, regular scatter tape was used to adhere and remove

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**Figure 1.** Schematic of continuous emulsions-to-particles formulation platform consisting of three modules: emulsion generation, perstraction, and incubation. In the (i) emulsion generation section, monodisperse dichloromethane emulsions containing the drug or drug−excipient mixtures were dispersed into a medium of immiscible aqueous continuous phase using a microtee. An additional stream of the aqueous continuous phase was added downstream of the emulsion generator to adjust the flow rates of the inlet stream for the pertractor. In the (ii) perstraction unit, a peroxide-cured silicone rubber tube (0.8 mm I.D.) was used as a tubular membrane for continuous extraction of the dichloromethane into a heated water bath at 48 °C. The droplet train moved in the tube in a laminar segmented flow. Dichloromethane solvent molecules, driven by the chemical potential gradient, left the droplets via diffusion into the aqueous continuous medium and across the silicone rubber membrane to the water bath which acted as a sink. The shrunk emulsions entered the (iii) incubation/solidification unit, which is a graham condenser with a 6 mm I.D. inner coil with an added inert nitrogen gas and aqueous diluting stream. A stratified gas−liquid flow configuration with the gas atop and a liquid layer containing the emulsions at the bottom of the coil was obtained. Silicone oil at 80 °C was recirculated in the shell as the heat exchange fluid. Digital images corresponding to the red boxes marked in the schematic capture (a) the emulsions within the silicone tube (perstraction unit), (b) stratified flow within the glass condenser coils, and (c) particles collected at the bottom of the condenser.
parts of the microparticles. Particle size distributions were obtained via digital image analysis (using ImageJ, NIH), in which 100 particles were measured for each formulation. Droplet shrinkage data were obtained via size measurements of 100 droplets using ImageJ, taken from each set of flow conditions at the three specified tube lengths. The DSC thermograms were obtained using a PerkinElmer Lab SYS-DSC 8500 apparatus. Around 5 mg of sample were crimped in a sealed aluminum pan and heated at 10 °C/min in the range of 100 to 280 °C using an empty sealed pan as a reference. Dry nitrogen was used as purge gas, and the N₂ flow rate was 50 mL/min.

3. RESULTS AND DISCUSSION

3.1. Continuous Emulsions-to-Particles Crystallization. We conducted continuous evaporative crystallization on emulsions containing drug or drug–excipient mixtures to yield spherical microparticles. The formulation platform consists of three different modules: emulsion generation, perstraction, and incubation/solidification. Each module has been included as part of the formulation platform for different purposes as elaborated below (Figure 1). A digital image of the benchtop platform may also be found in Section 1 of the Supporting Information (Figure S1).

In the emulsion generation section, a solution of drug or a drug–excipient mixture was first prepared in a selected solvent at desired concentrations and subsequently dispersed into an immiscible solvent using microfluidics, to segment the drug solution into monodisperse droplets carrying identical solution loads. Microfluidic emulsion generation has been well studied, and droplet sizes may be tuned according to the microfluidic device geometry, fluid properties, and flow rates. For our demonstration, we selected a dichloromethane-in-water emulsion system for the formulation of hydrophobic drug and drug–excipient microparticles, as we had previously identified it as a feasible system for microparticle production via thin-film evaporative crystallization. The monodisperse droplets were transferred into a silicone tube membrane submerged in heated water (perstraction unit), for continuous dichloromethane removal. The entire tube was immersed in a hot water bath (~700 mL) with the temperature set at 48 °C and with stirring set at 350 rpm.

In the perstraction section, volatile solvent in the droplets was subjected to a chemical potential gradient across the silicone tube. “Perstraction” is the selective permeation and extraction of a liquid component in the feed through a membrane phase, into an extracting liquid. The extracting liquid should be incapable of permeation through the membrane. Here, dissolved dichloromethane in the aqueous continuous phase selectively passes through the tubular silicone membrane and is extracted into the agitated water outside the tube. It is reported that water does not have favorable molecular interactions with silicone and is therefore a good extracting liquid. Due to the large volume of heated water surrounding the permeable tube and high agitation, the concentration of volatile solvent at the outer surface of the tube can be assumed to be negligible, and the water reservoir acts as a sink. Solvent molecules from the solute-laden dichloromethane droplet hence spontaneously diffuse into the aqueous continuous phase, and thereafter into the water bath through the silicone tube membrane down the chemical potential and concentration gradient. To further stabilize the emulsions, glycerol was added to make up 10 wt % of the aqueous continuous phase. Glycerol has also previously been used as an emulsion stabilizer for oil-in-glycerol systems. We note that the glycerol-PVA aqueous continuous phase fully wetted the walls of the silicone tube, allowing for the smooth transportation of droplets along the tube without coalescing. It was also observed that the large density difference (330 kg m⁻³) between the aqueous continuous phase and dichloromethane led to the sinking of droplets within the tube, and the droplets were observed to flow along the bottom half of the tube. The shrunken droplets were transferred out of the silicone tube, and into a third and final incubation unit before the onset of solidification, where nucleation and growth of the drug takes place. This last unit was used to complete the solidification process, even though it could be conducted in the silicone perstraction unit, as particles formed within the silicone perstraction tube were found to aggregate and adhere to the tube walls, especially for the case of small particles (<100 μm), leading to tube fouling. We have observed that when droplet volume reduction remains below 70%, the tubes remained clog-free, with droplets traveling down the tube length smoothly while shrinking (as shown in Figure 1a above). Beyond the 70% decrease in droplet volume, however, we observed an increased probability of tube clogging arising from the formation of particles within the tube that would adhere to the tube walls and induce secondary nucleation. Hence, solvent removal in this unit was limited to a 70% decrease in droplet size to reduce the possibility of particle fouling within the permeable tube.

The final incubation unit—a graham condenser—was used to create a stratified gas–liquid flow configuration within the vertically inclined glass coils. With the introduction of an inert gas flowing at 50 cm³/s, a stratified gas–liquid flow was formed with the gas atop and a liquid layer carrying the droplets at the bottom. This flow configuration was selected to accelerate residual dichloromethane solvent removal from the shrunken droplets and to provide a sink condition for residual dichloromethane to be flash extracted from the droplets. To complete the particle solidification step, the droplets were subjected to a higher degree of heating, to remove all residual dichloromethane from the droplets. Silicone oil was circulated in the shell at 80 °C. Here, solvent is removed from the droplets via diffusion through the thin film of continuous aqueous stream covering the droplets, before reaching the free surface between the coflowing gas and aqueous streams. Upon supersaturation, crystallization occurs within the shrunken droplets, which transforms them into solid microparticles while flowing along the glass coil. The solid microparticles that emerge from this unit are suspended in ultrapure water and underwent Büchner filtration thrice before they were dried under vacuum at room temperature for 8 h.

To ensure continuous lubrication to the base of the glass coil, an additional aqueous stream was added at the inlet of the condenser. This stream also served to address flow disruptions due to the high rate of solvent removal in this unit. As the rate of solvent removal was higher in this unit, the usage of surfactants could lead to an accumulation of stable bubbles trapped at the gas–liquid interface. Failure to remove these accumulated bubbles was observed to lead to uncontrolled pressure buildup in the condenser when the bubbles expanded to cover the entire inner diameter of the condenser coil, thus disrupting the flow. This additional aqueous stream effectively spread out the droplets flowing in the thin continuous liquid film and diluted the surfactant concentration in the aqueous

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liquid stream, reducing the likelihood and stability of bubbles formed. In addition, the glycerol present in the continuous phase also doubles as a water-based defoamer for the release of entrained dichloromethane bubbles at the gas–liquid interface.41

3.2. Generality of Platform for Different Types of Formulations. Using the above continuous platform, we formulated four types of hydrophobic drug and drug–excipient microparticles (as shown in Figure 2, experimental details are in the Experimental Section). The two colors observed on the microparticles in Figure 2D were due to the two different polymorphs that were present and ascertained by DSC analysis (see Figure S2 in Section 2 of the Supporting Information for details), to be the Y (a yellow thermodynamically stable polymorph) and ON (an orange kinetically stable polymorph). The dispersed phase flow rates were kept constant at 100 μL/min for all the microparticles produced, while the continuous phase flow rates were varied between 500 and 600 μL/min. The respective formulation compositions, initial droplet, and final particle size distributions are indicated in Table 1. The particle sizes can be controlled via the initial droplet sizes and solute loadings. A mass balance for a single droplet, which contains the drug, excipient, and solvent may be used to reason size trends for different solute loadings. During evaporation, only the solvent diffuses into the surrounding continuous phase whereas the solutes remain within the droplet until it solidifies (as it exhibits negligible solubility in the continuous phase). Therefore, for a droplet of constant size, the amount of solvent leaving from the droplet is lower in a high solute concentration laden droplet, resulting in a larger microparticle size. The microparticles were also tested for crystallinity using Differential Scanning Calorimetry (DSC). All drug and drug–excipient microparticles exhibited good crystallinity as seen from the sharp DSC peaks and PXRD data provided in the Supporting Information (see Figures S2 and S3 in Section 2 of the Supporting Information for details).

![Figure 2. Optical microscopy images of (a) GSK1, (b) GSK1-ethyl cellulose, (c) indomethacin-ethyl cellulose, (d) and ROY-poly(lactic-co-glycolic-acid) particles formulated using the continuous platform (flow conditions included in the Experimental Section).](image)

| Table 1. Total Solute Concentrations Used, Initial Droplet Sizes, and Final Particle Sizes for the Four Different Formulations Tried |
|---|---|---|
| Formulation | Total solute (drug and excipient) loading (mg/mL) | Initial droplet sizes (μm) | Final particle sizes (μm) |
| A. GSK1 | 16 | 275 ± 9 | 70 ± 12 |
| B. GSK1-ethyl cellulose | 21 | 280 ± 7 | 186 ± 6 |
| C. Indomethacin-ethyl cellulose | 100 | 275 ± 9 | 170 ± 18 |
| D. ROY-poly(lactic-co-glycolic-acid) | 280 | 457 ± 10 | 330 ± 43 |

Depending on the drug solubility in various solvents obtained during the drug screening process, an appropriate emulsion system may be designed accordingly for implementation. The main considerations for an appropriate emulsion system are high drug and/or excipient solubility in the dispersed phase solvents, low (ideally zero) drug/excipient solubility in the continuous phase, and immiscibility of the dispersed and continuous phases. For example, this system may be adapted for the formulation of hydrophilic drugs, by implementing a water-in-oil emulsion system, tuning the temperatures of the perstraction and solidification unit.42 In addition, a different polymeric membrane might have to be used specifically for the removal of water through a continuous phase with a higher boiling point (such as dodecane or mineral or silicone oil), at overall higher bath temperatures. Ceramic membranes which have been used to selectively remove water
3.3. Modeling Droplet Size Change. To predict the rate of solvent removal from droplets and hence the evolution of droplet size across the continuous evaporative crystallization platform, we formulated a mass transport model for dichloromethane removal from the perstraction unit. The detailed mass transport equations and a discussion of the experimental and theoretical shrinkage trends across the pertractor unit may be found in Section 3 of the Supporting Information. Solvent removal within the condenser unit was not included in this model as the organic solvent was flashed from the droplets due to the elevated operating temperature of the unit (at twice the boiling point of dichloromethane). In the case of the use of a cosolvent as the dispersed phase, we can expect an initially faster shrinkage, as methanol is miscible with water and escapes nearly instantaneously.

Briefly, the simplified mass transport model for perstraction is described in two key steps: (i) the mass transfer of dichloromethane from the dichloromethane–water interface to the silicone tube inner wall and (ii) the transport of dichloromethane across the silicone tube membrane. Due to the large volume of water and high agitation from stirring in the water bath, we neglected the transport of dichloromethane from the outer surface of the tube to the free surface of the water and simply assumed the water bath to be a sink. The mass transfer resistances from the two aforementioned steps were calculated and compared, and the rate-limiting step for dichloromethane diffusion was determined to be the transport across the silicone tube membrane. At steady state, the overall molar diffusive flux of dichloromethane in the silicone tube membrane \( J_p \) expressed in cylindrical coordinates is

\[
J_p = \frac{D_m}{R_i \ln \left( \frac{R_i + l_t}{R_i} \right)} C_{sat}
\]

where \( R_i \) is the inner radius of the silicone tube (m), \( l_t \) is the thickness of the silicone tube membrane (m), \( D_m \) is the effective diffusivity of dichloromethane in silicone rubber \( (m^2 s^{-1}) \), and \( C_{sat} \) is the solubility of dichloromethane in water \( (mol m^{-3}) \).

Coupling the flux across the membrane to the mass balance of dichloromethane yields the rate of change of droplet size with time. The normalized change in droplet volume for a single droplet traveling along the silicone tube as a function of time is shown below.

\[
\left( \frac{r}{r_0} \right)^3 = 1 - \frac{2FMD_m C_{sat}}{R_i^2 \rho \ln \left( \frac{R_i + l_t}{R_i} \right)}
\]

where \( r \) and \( r_0 \) are the droplet radius and initial droplet radius (m), \( F \) is the flow ratio between the continuous and the dispersed phase, and \( t \) is the time \((s)\) the droplet spends in the silicone tube.

A series of flow studies were conducted to validate the droplet shrinkage model across the perstraction unit, using silicone tubes with the same inner diameter \( (R_i) \) and same flow conditions but varying tube wall thickness \( (l_t) \). Perstraction was also conducted at the same water bath temperature of 48 °C. Size measurements of droplets were conducted at 0, 2, and 4 m along the tubes, and flow rates were varied to tune the residence time of the droplets. For the same flow conditions \((F = 6, 8, 12)\) and initial droplet diameters \((450 \mu m)\), the experimental trends showed no significant difference in droplet shrinkage with time despite the doubling of silicone tube wall thickness (shown in Figure 3). Both trends collapsed to give a gradient of \( \sim 3.7 \times 10^{-3} s^{-1} \), which translates to a decrease of \( \sim 0.4\% \) in droplet volume per second. A linear fit of \( D_m \) (the diffusivity of dichloromethane in the silicone tube membrane) to the experimental trends obtained from the gradient of linear plot \( \left( \frac{r}{r_0} \right)^3 \) against \( t \) for different values of \( F \) gave average values of \( 3.34 \times 10^{-12} m^2 s^{-1} \) and \( 4.90 \times 10^{-12} m^2 s^{-1} \) for the silicone tubes with 0.8 mm and 1.6 mm wall thickness respectively, which is in the range of typical diffusivity values \((10^{-8} to 10^{-12}) m^2 s^{-1}) \) for organic solvents across rubbery membranes.44 The order of magnitude of dichloromethane diffusivity obtained (smaller than the initial \( 10^{-10} m^2 s^{-1} \) used for determining the mass transfer limiting step in eqs S3 and S5 in Section 3 of the Supporting Information) further validated the assumption that the mass transfer of dichloromethane in the system was indeed limited by the transport across the silicone tube membrane.

We attribute the difference in estimated diffusivity of dichloromethane for the two different tube thicknesses of the same wall material to manufacturing differences.

3.4. Throughput of Continuous Platform and Scale-Up. With a single process line consisting of a 4 m silicone tube and 600 mm off-the-shelf graham condenser, the continuous formulation platform currently operates at a dispersed volumetric flow rate of 0.15 L/day without fouling. The throughput of the system is dependent on two factors: the rate of solvent removal from the pertractor and the incubation unit under conditions of regular flow, as well as the solubility of the drug in the dispersed phase.

![Figure 3. Experimental droplet shrinkage across the two silicone tubes with 0.8 mm and 1.6 mm wall thickness. The y axis is the normalized droplet volume expressed as \( \left( \frac{r}{r_0} \right)^3 \) and the x axis is time (t) in seconds. The analytical expression (eq S10) is shown in the figure, where the gradient is a function of F (the ratio of aqueous continuous phase to dichloromethane at the silicone tube inlet), \( D_m \) (diffusivity of dichloromethane in water, \( m^2 s^{-1}) \), \( C_{sat} \) (solubility of dichloromethane in water, \( g m^{-3}) \), \( R_i \) (radius of silicone tube, m), and \( l_t \) (silicone tube thickness, m). The dotted lines are linear fits to the experimental droplet shrinkage from perstraction in the 0.8 mm thick silicone tube (●) and 1.6 mm thick silicone tube (○). The initial droplet diameter is 450 μm.](Image 324x536 to 564x694)
First and foremost, it is essential for flow regularity to be maintained in both perstraction and incubation units for controlled production of spherical microparticles. This necessitates the removal of bubbles from the system. The rate of solvent removal in the perstraction may be controlled by temperature and the flow rates of continuous to dispersed phases. We found that dichloromethane could be successfully removed from the droplets without bubble formation when operating in the water bath temperature range of 45–50 °C; any temperatures above 50 °C led to uncontrolled bubble formation within the silicone tube. Also, the loss of dichloromethane over time leads to a reduction in flow velocity of the droplets, leading to a pileup of droplets. The pileup creates local regions with high dichloromethane concentrations and favors the formation of dichloromethane bubbles, which disrupts the laminar flow. The ratio of continuous to dispersed phase flow rates of greater or equal to 5x is recommended. This in turn has two effects: the loss of dichloromethane from droplets does not have a major impact on the flow velocity in the perstraction tubes, which prevents droplet pileup, and sufficient spacing can be maintained between adjacent droplets. Likewise for the condenser, a dilution stream is recommended to space the droplets out and prevent emulsion or particle pileup from occurring within the condenser during solidification. Bubble nucleation and growth may be controlled by adjusting the rate of solvent removal via temperature, flow rate of gas, height of water film covering the emulsions, or composition of continuous phase surrounding the emulsions. Finally, particle formation should not disrupt the flow of the continuous medium which transports the particles downstream within the condenser. For a 4 m, 0.8 mm I.D. silicone tube perstraction unit, recommended operating parameters for particle production are a dispersed phase flow rate of 0.15 L/day (for initial droplet diameters of 400–600 μm) immersed in a water bath with the temperature kept between 45 and 48 °C. For a 600 mm effective length, 30 coils, 6 mm I.D. glass condenser, the recommended operating parameters are a gas flow rate of 2750 sccm and a liquid flow rate of 1.9–4.8 L/day with silicone oil circulating in the shell at 65–75 °C. We note that there are multiple parameters within each module which can be optimized. However, a detailed full optimization of the complex multidimensional operating parameter space for this entire system is dependent on the selected emulsion system and well beyond the scope of this proof of concept demonstration. Currently, the volumetric throughput of the system is dependent on the maximum rate of mass transfer of dichloromethane removed without disrupting flow regularity due to bubble evolution within the process line. Scaling out (by parallelization) of the silicone tube and condenser will however enable greater solvent removal and hence increase volumetric and mass throughput. The condenser unit, upon scaling up by custom design and manufacture, will also be able to handle higher dichloromethane removal loads. One can simply envision 3D printed coils with larger diameters and longer coil lengths for handling higher volumes of emulsions. The mass throughput of the various formulations depends on the solubility of the selected drug and excipient in the dispersed phase solvent. Drugs with low solubility in dichloromethane such as GSK1 (3.5 mg/mL dichloromethane) have a mass throughput of 0.5 g/day, while formulations with drugs exhibiting higher solubility in dichloromethane such as ROY (580 mg/mL dichloromethane) will translate to higher mass throughputs of ~80 g/day per line.

4. CONCLUSION

We have demonstrated a novel evaporative emulsion crystallization platform for producing spherical drug microparticles with tunable compositions and sizes. Herein, we have discussed the design components of our continuous evaporative formulation platform, which consists of three sections to ensure the creation of spherical drug microparticles. The platform utilizes microfluidics to first generate monodisperse emulsions loaded with the active ingredient/excipient solution, before subjecting the emulsions to continuous evaporative emulsion crystallization in two solvent removal units (a silicone tube and glass condenser), generating supersaturation for particle solidification. We demonstrate the formulation of four different pharmaceutical microparticles (shown in Figure 2) using two solvent systems of dichloromethane-in-water and dichloromethane/methanol-in-water. We also discuss the mass transfer of dichloromethane solvent from the droplets, predicting the change in droplet sizes across the perstraction unit. Finally, we discuss the achieved process throughput and routes to increase them and provide some recommendations and considerations for smooth operation and scaleup.

## ASSOCIATED CONTENT

### Supporting Information

- [Digital Image of Experimental Setup.](#)
- [Polymeric Characterization of Formulated Microparticles.](#)
- [Modeling Droplet Size Change](#)

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**Notes**

The authors declare no competing financial interest.

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### LIST OF SYMBOLS

- $r$, $r_0$ - droplet radius and initial droplet radius (m)
- $R_w$, $l$ - radius and wall thickness of silicone tube (m)
- $J_d$ - diffusion flux of dichloromethane in the perstraction unit (mol/m² s)
- $t$ - time elapsed (s)
- $C$, $C_{sat}$ - concentration and saturated concentration of dichloromethane in water respectively (mol/m³)
- $Q_{w}$, $Q_{dcm}$ - volumetric flow rate of water and dichloromethane in the perstraction unit (silicone tube) (m³/s)
- $D$ - diffusivity of dichloromethane in water (m²/s)
- $F$ - volume ratio of aqueous continuous phase to dichloromethane
M - molecular weight of dichloromethane (g/mol)
ρ - density of dichloromethane (kg/m³)
h - height of aqueous film in condenser coil (m)

■ REFERENCES