On the use of a twin screw extruder for continuous solid feeding and dissolution for continuous flow processes

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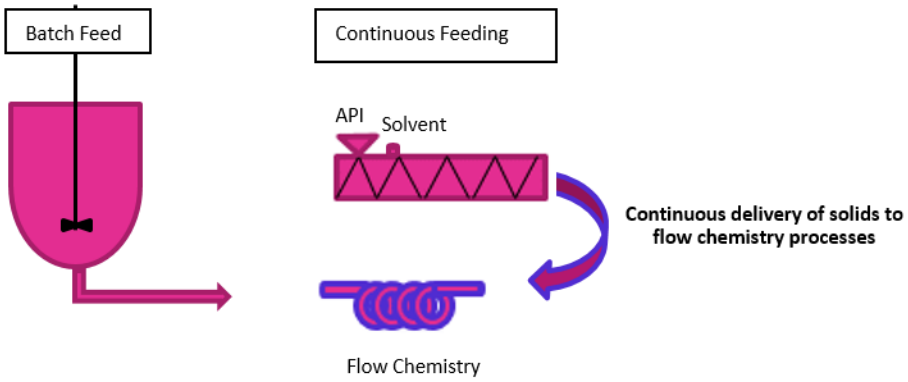
ABSTRACT

The progress from batch to continuous manufacture of pharmaceuticals has highlighted the challenging area of dosing solid material directly, efficiently and accurately into continuous flow systems for work up in flow chemistry processes. Twin screw extruders (TSE) have the advantage of decoupling the dry (loss in weight feeder end) with the wet (liquid input) to prevent solids from sticking around the feeder thereby enabling continuous solid feeding into a flow process. In this study, the feasibility of a 16mm TSE as a solid feeder is investigated and efficient dissolution of an example API is demonstrated. Paracetamol and an 80:20 mixture of water and IPA are the solute

and solvent respectively. The concentrations of paracetamol during dissolution experiments are monitored using an in-line UV-ATR probe connected to a spectrometer, and dissolution kinetics are extracted. Full dissolution of powder particles is obtained within the residence time of the TSE, however full dissolution of granular particles is achievable by lowering feed rates or having higher barrel temperatures. We have, for the first time, proposed a methodology of estimating the power density for TSE, this enables a fair comparison of dissolution rates between this continuous system and a batch stirred tank.



INTRODUCTION

Continuous manufacturing in pharmaceutical industry has gained significant attractions recently as it offers potential flexibility, quality and economic advantages over batch operation [1-3]; substantial research in reaction, crystallisation and filtration have been reported in the past decade [4-8], however, continuous work up, e.g. solid dissolution and dosing, remains a challenging area yet to be addressed. The introduction of raw materials and intermediates for continuous pharmaceutical manufacturing processes are currently based on batch feed systems, e.g. using stirred tank vessels for dissolution of solid particles [9, 10]. Depending on the physical properties of the solids, such as non-wetting (hydrophobic), clumping or floating, dissolution of solids in batch

vessels is often a labour intensive and time consuming operation, with common problems involving mass transfer limitation for solids dissolution, non-uniformity of slurry composition on discharge, and nozzles plugged by solids. For suspension of sinking solids, adequate mixing for off-bottom suspension of particles is essential, this however leads to overmixing overall, potentially causing foaming in solid-liquid suspensions, reducing dissolution characteristics [11].

For suspension of floating solids, entrainment is often achieved using a mixer designed to provide downward pulling drag force to offset the upward buoyancy force, leading to incomplete solids wetting, shearing and breaking up of agglomerates [12, 13]. If solids are sticky, agglomeration and accumulation on the impellers, baffles and supports are the norm, leading to batch to batch variation on product quality.

The use of static mixers has addressed various mixing issues [14, 15], including solids blending in a fluid phase, the dispersion of additives in a suspension, and solid dispersion by breaking agglomerates in a fluid phase and in pulp and paper processes [16]. There are however still problems in maintaining slurry homogeneity in flow, resulting blockages in valves and nozzles during downstream processing when solids are present. A continuous solid dosing system incorporating complete dissolution would overcome the above issues; this is the focus of our work where a twin screw extruder is investigated as a novel solid dosing and dissolution system. Twin screw extruders have extensively been studied for Hot Melt Extrusion (HME) [17-20] and wet granulation [21-26]. The objectives of this work are to design and adopt the twin screw extruder as a continuous dissolution system; to carry out a systemic investigation of the effects of design and operational parameters

on solid dissolution; to gain scientific understanding on dissolution kinetics and to establish a comparison on dissolution kinetics between batch and continuous dosing systems.

EXPERIMENTAL SECTION

MATERIALS

Two grades (powder and granular) of paracetamol (99% purity) were supplied by Mallinckrodt Chemical Limited (UK). The mean particle size and particle size distributions (see Figure 1) were analysed by a Mastersizer 3000™ (HYDRO, Malvern) and given in Table 1. Raw materials, directly purchased from the manufacturer, were powders not agglomerates. The samples were dispersed in hexane and added directly to the Malvern.

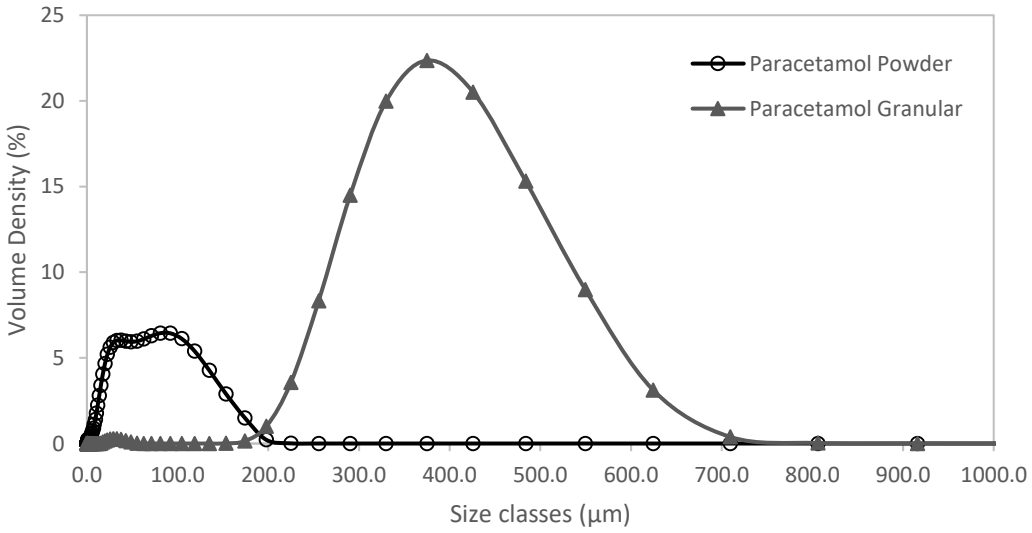


Figure 1 Particle size distribution of powder and granular paracetamol

Table 1 Particle sizes for two types of paracetamol

	Dx (10) (μm)	Dx (50) (μm)	Dx (90) (μm)
Powder	12.6	44.9	124
Granular	263	374	516

Propan-2-ol (IPA) (>99.5% purity) was sourced from Sigma-Aldrich (Gillingham, UK). Deionised water was produced using the in-house Millipore Milli-Q system.

METHODS

Flow Properties

FT4 Powder Rheometer (Freeman Technology Ltd., Tewkesbury, UK) was used to measure bulk properties and dynamic flow for each of the grades of paracetamol including 1) Stability and Variable Flow, 2) Permeability, 3) Aeration, 4) Compressibility and 5) Shear Cell 9kPa. All tests were conducted in 25mm cells. Data was collected using the FT4 Powder Rheometer software version 4.0 (Freeman Technology Ltd., Tewkesbury, UK) and analysed with FT4 Data Analysis software version 3.01.0057 (Freeman Technology Ltd., Tewkesbury, UK).

Continuous Twin Screw Extruder

A 16mm diameter twin screw extruder (TSE) (Eurolab 16, Thermo Fisher Scientific, Stone, UK) is shown schematically in Figure 2. The barrel has a length of 400 mm with a length to diameter ratio of 25:1. Liquids are dispensed into the barrel using a peristaltic pump (Watson Marlow,

Falmouth, UK) and solids added via a loss in weight (LIW) gravimetric feeder. Two types of feeders were used in this work including a Brabender MT-S LIW Feeder and a Brabender FW-18 Flexwall Classic LIW Feeder (see Figure 3). The former is a rigid frame laboratory scale feeder with twin concave screws suitable for low feed rates (< 10 g min^{-1}) of high bulk density materials (e.g. granular paracetamol), while the latter is a universal flexible wall feeder with a single spiral screw suitable for materials with poor flowability and low bulk density (e.g. powder paracetamol).

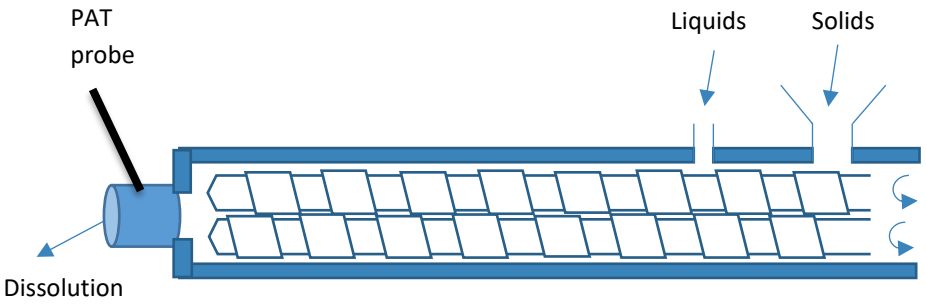


Figure 2 Schematic of continuous twin screw extruder

The extruder is connected to a central control unit where temperature and screw speed can be varied. The temperatures of different sections along the barrel are controlled by electrical heating bands and monitored by thermocouples. A bespoke discharge coupling, and tubing was connected to the exit of the twin screw to provide downward output of material. This prevented build-up of material at the extruder exit. The UV probe was mounted on a retort stand and inserted into the tubing. Absorbance data is collected continuously using a UV-ATR probe inserted at the flow exit, interfaced with a Carl Zeiss MC600 Spectrometer and a PC for real-time display, logging and data analysis.

The residence time of liquid within the barrel was measured to aid the determination of dissolution kinetics. A dye was injected at liquid entry ports and minimum residence times of the dye were recorded. When liquid enters the barrel at port 6, the residence time is merely 3 seconds, which is the same as the UV probe capture time, hence the UV probe is insufficient to allow direct measurement for this case, a digital stopwatch was used instead. The variations obtained were $\pm$ 0.2 seconds for five measurements.

Figure 3 Set up of continuous twin screw extruder with LIW gravimetric feeders

In dissolution work, solids are dosed at Port 1 of the barrel as shown in Figure 4; liquid flows from the right to left and can be pumped in at any of the Ports from 2 to 6 (see Figure 4). In this

way, the decoupling of the dry solids from the wet liquid is achieved, preventing solids from sticking around the feeder. Liquid coming at Port 2 has the longest residence time of 13 seconds within the barrel whereas liquid at Port 6 the shortest residence time of 3 seconds.

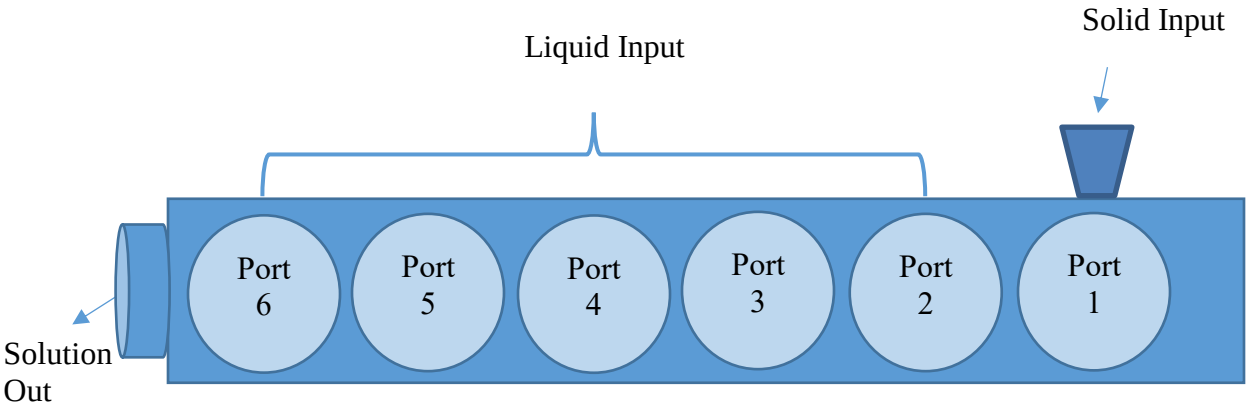


Figure 4 Schematic of barrel showing input port positions

In order to obtain a concentration-time profile, calibration curves of absorbance versus concentration were generated from known amounts of paracetamol in the Water/IPA (80:20) solvent system, with a maximum absorbance peak at 248nm. A complete set of sequential runs were then undertaken at each port, e.g. Run 1 at Port 6, Run 2 at Port 5, Run 3 at Port 4, and so on, due to the short residence time. The absorbance measurements were recorded using the in-line UV-ATR probe positioned at the TSE exit. Compiling the output concentrations at each port, a dissolution profile was finally assembled.

RESULTS AND DISCUSSION

Material Characterisation

In order to feed solids consistently and accurately in continuous manufacturing processes even at small flow rates (< 5 g min^{-1}), the choice of feeder is of utmost importance, as feeder's performance is strongly dependent upon flow properties of materials [27], for instance, the use of LIW feeders improved the ability to control feed rates for powders with high cohesion and electrostatics [28]; the use of flexible frame LIW feeders with a single spiral screw was good for materials with low bulk density and poor flow ability [26]. For materials with higher values of bulk density (0.5 g ml^{-1}), a rigid frame LIW feeder with concave twin screws worked well.

Prior to the decision of feeder and screw used in this study, the flow properties of powder and granular paracetamol were determined using the FT4 Powder Rheometer as listed in Table 2.

Table 2 Particle properties of paracetamol

	Mean Particle Size (μm)	Bulk Density (g ml^{-1})	Permeability (cm^2)	Basic Flowability Energy (mJ)	Compressibility (% @ 15kPa)	Cohesion (kPa)
Granular	374	0.728	$6.6x10^{-5}$	630.2	29.1	0.49
Powder	45	0.357	$4.1x10^{-6}$	150.3	51.7	1.68

It is clear that powder has lower bulk density and poorer flow properties (indicated by the numbers of the Basic Flowability Energy) than granular; while granular has a lower %

compressibility suggesting that this is a non-cohesive material which is less likely to compact on the feeder. The stability and variable flow tests indicated that two grades of the paracetamol did not show any signs of de-agglomeration or segregation and were stable during flow, although the powder was more sensitive to changes in flow rate, mainly as a result of high air content in the cohesive material. The measurements were made on the different feeders and in combination with the FT4, an agreement with previous work [26-28] is seen.

Dosing trials at a solid feed rate of 3.33 g min^{-1} confirmed the above selections as the other combinations caused significant problems, e.g. the single spiral screw was unable to convey granular paracetamol due to an increase in the frictional resistance to flow because of entrainment, alarming feeder and shutting down the operation. Likewise, the powder presented challenges in the rigid frame feeder due to the increase in torque that has compacted powder within and between the screws, as well as the barrel housing. This also led to the feeder shutting down.

Dissolution tests

The solubility for paracetamol in water/IPA (80:20) at 40˚C is 11g paracetamol in 100g of solvent [29], i.e. at a solid: liquid ratio of 1:9. The dissolution tests were carried out at a solid: liquid ratio of 1:11 to ensure complete dissolution. Paracetamol powder was continuously dosed into the TSE using the single screw flexible wall LIW feeder at a feed rate of 3.33 g min^{-1} and the solvent (Water/IPA 80:20) at a flow rate of 37 g min^{-1}, giving a target output concentration of 9.0 g per 100 g solvent. Figure 5 shows that complete dissolution was obtained within the residence time of

the barrel (13 seconds) where the concentration of paracetamol at the exit was consistently 9.0 g $\pm$ 0.1 g per 100 g solvent (see Figure 5).

The same tests were carried out for granular paracetamol using a twin screw rigid wall LIW feeder at the same feed rates, complete dissolution was not achieved within the residence time of the barrel (see Figure 5) with some undissolved paracetamol being observed in the exit. The concentration of paracetamol in the exit remained at 7.7 $\pm$ 0.3 g per 100 g solvent for 3000 seconds. 160 seconds run time for granular paracetamol is plotted for the purpose of comparison with that for powder paracetamol.

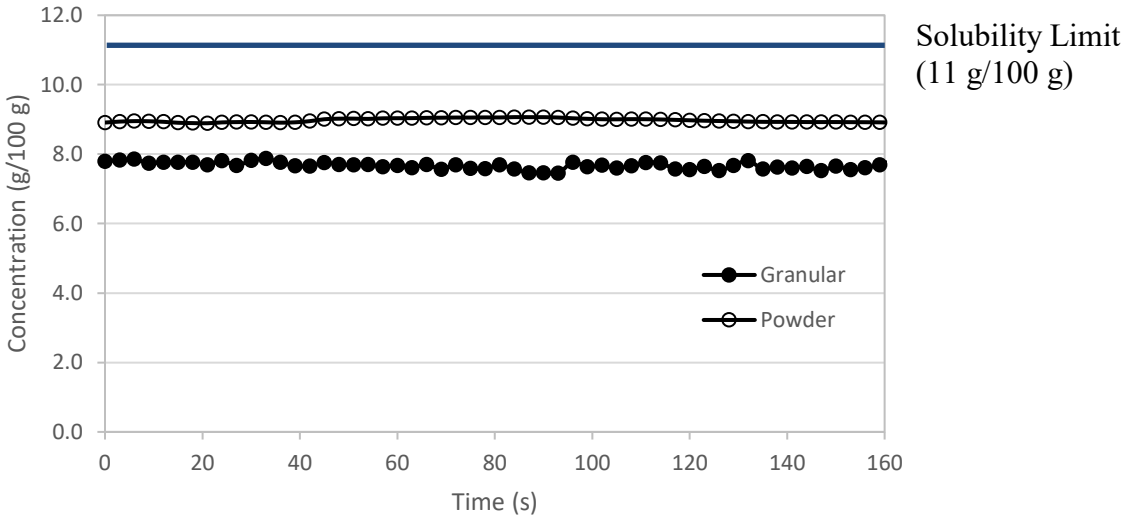


Figure 5 Concentration-time profile post TSE for dissolution of paracetamol (Temperature = 40˚C, solid feed rate = 3.33 g min^{-1}, liquid flow rate = 37 g min^{-1})

Dissolution tests were carried out at a solid feed rate of 2.5 g min^{-1} and a liquid flow rate of 29 g min^{-1}, giving a target output concentration of 8.6 g per 100 g solvent. Dissolution profiles were compiled from the concentrations at exit of the TSE for liquid input at each port as shown in Figure 6. Note that each concentration measurement was repeated 3 times and the data in Figure 5 are the averaged value from three repeats. Error bars are not shown on the graph as they are too small to see clearly. The variation obtained for the runs at each port are given for granular paracetamol - standard error 0.2, 0.3, 0.2, 0.2, and 0.1.

We see that both grades gradually dissolve along the barrel of the TSE with faster and fuller for powder than for granular grade, which is consistent with what has been shown in Figure 5 as well as previous work [30] in a stirred tank vessel.

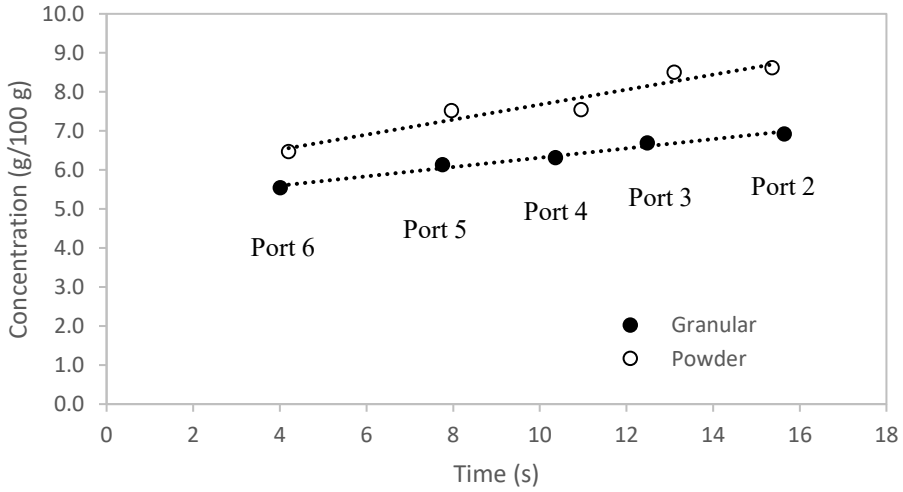


Figure 6 Dissolution profile for paracetamol dissolution (Temperature = 40˚C, solid feed rate = 2.5 g min^{-1}, liquid flow rate = 29 g min^{-1})

Dissolution Kinetics

Fitting the first order kinetics, Figure 7 plots of ln (C2/C1) vs time where C2 and C1 are the concentrations of paracetamol (g $100g^{-1}$) at the starting and dissolution times. The straight line fit confirms the first order kinetics and the slope of which gives the rate constant of dissolution k = 0.0162 s^{-1} and 0.0211 s^{-1} for granular and powder respectively.

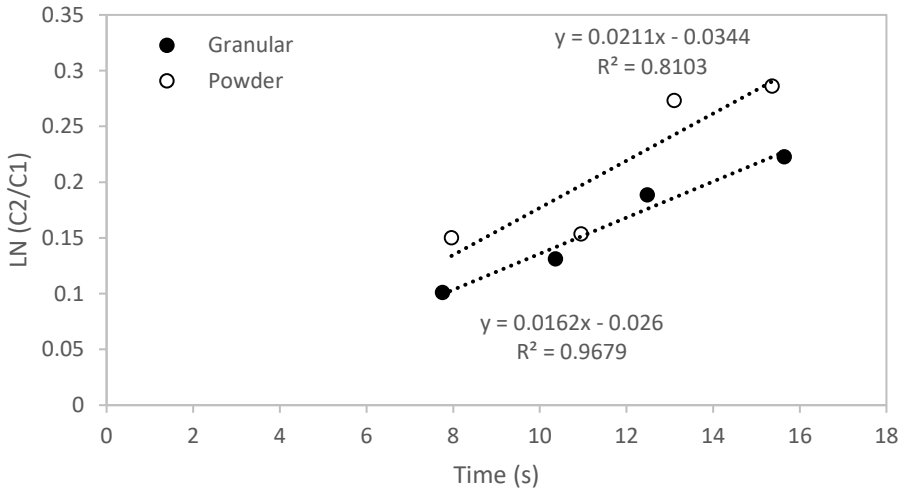


Figure 7 Dissolution kinetic plots of ln (C2/C1) vs time for granular and powder paracetamol

Achieving full dissolution

From Figure 6, we see that the granular paracetamol does not fully dissolve within the residence time of the barrel. The target concentration for full dissolution at the set feed rates (2.5 g min^{-1}

solid and 29 g min^{-1} liquid) is 8.6 g (paracetamol)/100 g (solvent). This was achieved for powder grade but not for granular where 6.9 g (paracetamol)/100 g (solvent) was dissolved. Several operational parameters in the TSE can however be manipulated to afford full dissolution, including liquid flow rate, solid feed rate, screw speed, screw configuration and barrel temperature. These parameters are investigated in turn.

Effect of Liquid Flow Rate

At a fixed solid feed rate of 2.5 g min^{-1} and a fixed solution temperature of 40˚C, Figure 8 shows the dissolution concentrations for various liquid flow rates from 15 to 35 g min^{-1}. Increasing liquid flow rates to achieve sink conditions results in a higher driving force for dissolution but reduces the residence time for mixing within the barrel as the degree of screw fill is higher. Increasing the liquid feed rate decreases the concentration of the output solution and does not achieved full dissolution of the solute. Solvent flow affects the dissolution process by physical abrasion of the solid, thereby reducing the diffusion layer thickness around each particle [31]. The decrease of liquid flow rate increases the residence time within the barrel from 11 to 15 seconds allowing more time for dissolution. Table 3 shows the correlations between the solid/liquid feed rates and concentrations.

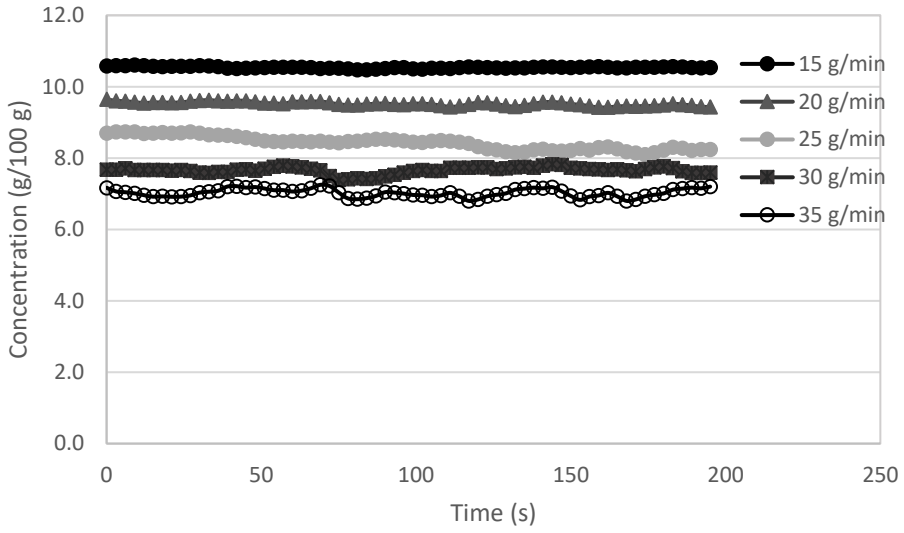


Figure 8 Concentration-time profile of granular paracetamol in water/IPA (80:20) (Temp=40°C, solid feed rate = 2.5 g min^{-1}).

Table 3 Correlations between concentrations and liquid flow rate at fixed solid feed rates

Solid flow rate (g/min)	**Liquid flow rate (g/min)**	**Target Concentration at full dissolution (g solute/100 g solvent)**	**Actual Concentration (g solute/100 g solvent)**	**Maximum Dissolution Achieved**	**% Dissolved**
2.5	15	10.7 (saturated)	10.6	Yes	99
2.5	20	10.7 (saturated)	9.6	No	90
2.5	25	10.0	8.4	No	84
2.5	30	8.3	7.7	No	93
2.5	35	7.1	6.5	No	92

Effect of Solid Feed Rates

At a fixed liquid flow rate of 30 g min^{-1} (at which full dissolution was not achievable) and at a fixed solution temperature of 40 ˚C, Figure 9 shows the effect of varying solid feed rates on the dissolution concentration. Increasing the solid feed rate increases the concentration of the output solution but does not achieve full dissolution of the solute. Decreasing the solid feed rate from 3.33 g min^{-1} to 1.05 g min^{-1} decreases the saturation level of the solution and the degree of screw fill. The TSE is a starve fed system hence when the throughput is decreased at constant rpm more mixing occurs as the materials being processed have a longer residence time in the mixing elements. Full dissolution was achieved at 1.67 g min^{-1}. Table 4 shows the correlations between the solid/liquid feed rates and concentrations.

Drug development studies are often carried out with limited amount of materials, the lowest feed rate of solids is thus of significant interest for this type of work. Our tests show that the lowest feed rate of solids for the TSE producing consistent concentrations measurements at the exit was 1.67 g min^{-1}. Observations in this study indicate more variability in the exit concentration with decreasing feed rate.

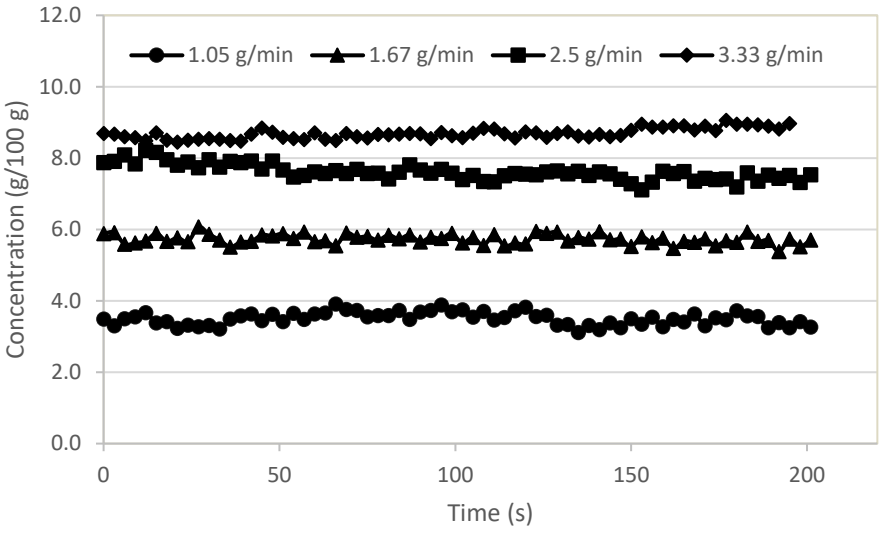


Figure 9 Concentration-time profile of granular paracetamol in water/IPA (80:20)

(Temp=40°C, liquid flow rate = 30 g min^{-1})

Table 4 Correlations between concentrations and solid feed rate at fixed liquid flow rates

Solid feed rate (g/min)	Liquid flow rate (g/min)	Target Concentration at full dissolution (g solute/100 g solvent)	Actual Concentration (g solute/100 g solvent)	Maximum Dissolution Achieved	% Dissolved
3.33	30	10.7 (saturated)	8.7	No	81
2.5	30	8.3	7.6	No	92
1.67	30	5.6	5.7	Yes	100
1.05	30	3.5	3.5	Yes	100

Effect of Screw Speed

The screw in the TSE conveys the solids forward and the speed of which can affect dissolution rate. The investigations were carried out for the screw speed from 100 to 500rpm (50 rpm resulted in accumulation of solids at the input port) at a fixed liquid flow rate of 30 g min^{-1}, a fixed solid feed rate of 2.5 g min^{-1} and a solution temperature of 40˚C. The target concentration for full dissolution at the set feed rates is 8.3 g (paracetamol)/100 g (solvent). While shear mixing and power consumption intensify with the increase of the screw speed, allowing solute molecules to encounter fresh solvent molecules faster, dissolution rate does not change significantly and complete dissolution of granular paracetamol was not achieved by increasing the screw speed alone. This is due to the fact that the residence time of the solute within the barrel is reduced as the screw speed is increased (see Table 5).

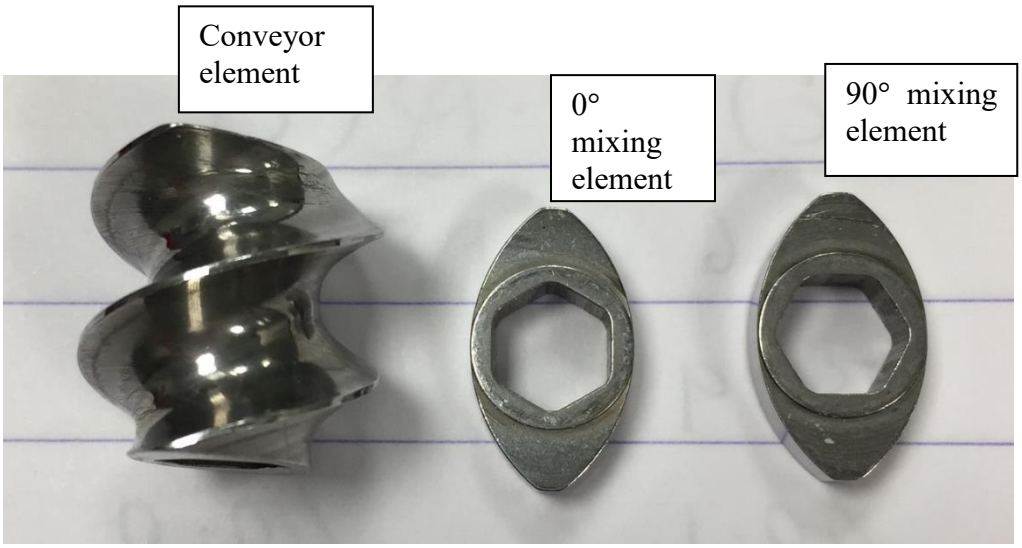
Table 5 Effect of screw speed on residence time

Screw Speed (rpm)	Mean Concentration of Paracetamol in Solution (g 100 g^{-1})	Residence Time (s)
100	7.9	13.2
200	7.1	8.8
300	7.5	6.9
400	7.8	6.7
500	8.1	6.0

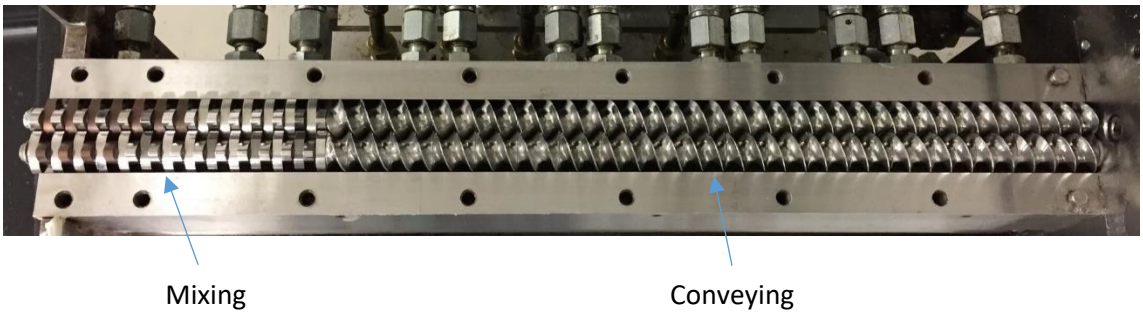
Effect of screw configuration

The twin screws in the TSE are made up of individual elements of either concave conveying or bi-lobe mixing (see Figure 10A), delivering different shear energy to the materials. The effect of the screw configuration on dissolution was investigated by using one, two and three mixing elements

at the discharge (left) end of the screws (Figure 10B), i.e. at Ports 5 and 6 (Figure 4). The dissolution profile is shown in Figure 11. Adding mixing elements to the screw configuration increases dissolution, more for Ports 6-5 than the earlier ones, due to the increase in shear mixing. The impact on residence time of solute within the barrel was < 2 seconds. Complete dissolution of the granular paracetamol was not attained for any mixing elements, however more consistent concentration of solution is obtained with more mixing elements.



(A)



(B)

Figure 10 (A) - Conveying and Mixing Elements, (B) twin screws within the barrel

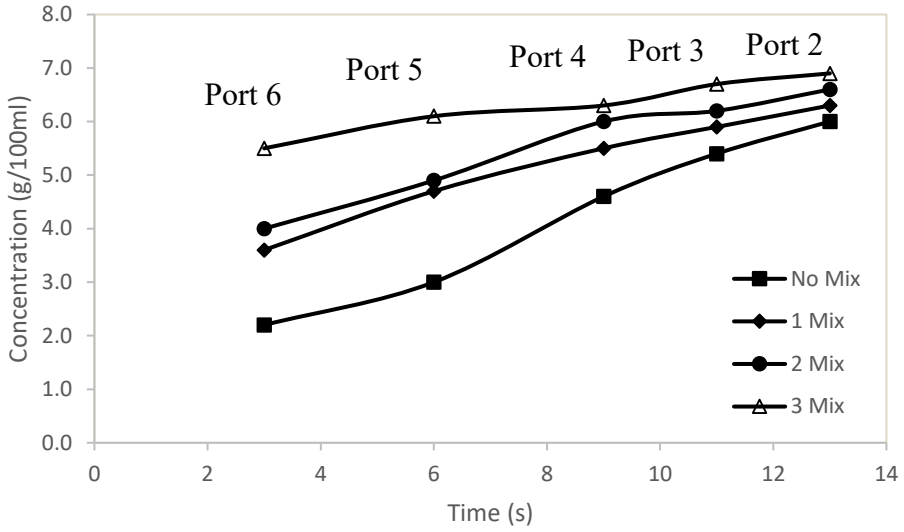


Figure 11 Effect of adding mixing elements on dissolution profiles (Temperature = 40˚C, solid feed rate = 2.5 g min^{-1}, liquid flow rate = 30 g min^{-1}, screw speed = 100 rpm)

Effect of Barrel Temperature

The barrel is effectively a heating jacket and temperatures in each of the sections (Port 2 to Port 6) can individually or collectively be controlled. Figure 12 shows the effect of barrel temperature on dissolution from room temperature to 75°C. It is expected that an increase in barrel temperature enhances dissolution and full dissolution of the granular paracetamol was achieved when the barrel temperature reached 60°C.

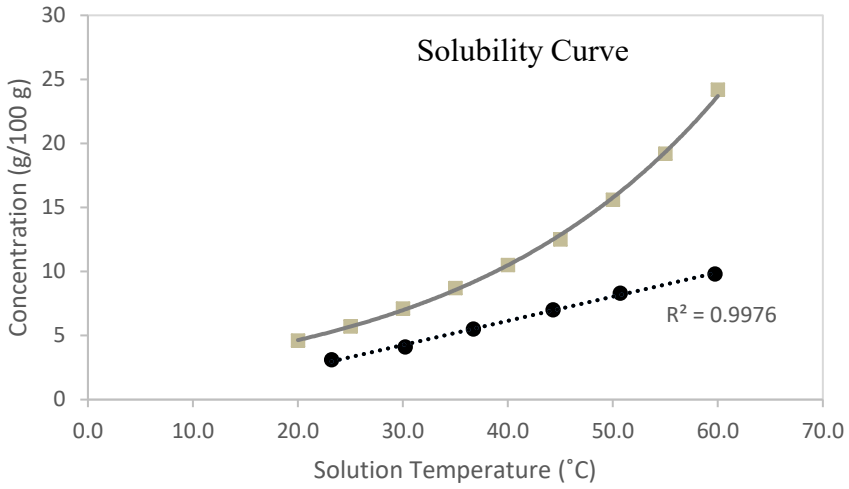


Figure 12 Effect of barrel temperature on dissolution of paracetamol (solid feed rate = 2.5 g min^{-1}, liquid flow rate = 30 g min^{-1}, screw speed = 100 rpm), Solubility curve overlaid

In summary, the flow rates of either liquid or solid together with the barrel temperature can lead to complete dissolution of granular paracetamol.

Batch v Continuous Dissolution

Dissolution of solid materials in a batch vessel is the current norm for feeding in the pharmaceutical industry, we carried out the same dissolution experiments in a stirred tank (temp = 40 ˚C, agitation rate = 750 rpm, mass of solute = 83 g, mass of solvent = 1000 g) and compare the dissolution profiles in Figure 13. It is clear that dissolution is much faster in the TSE than that in the stirred tank vessel, e.g. 13 seconds to dissolve 83g of paracetamol vs. 126 seconds to dissolve the same. The increase in the dissolution rate in the TSE is due to much more aggressive local shear mixing

and higher thermal energy generated by the rotation of the screws [32]. This also delivers good uniformity of the solute in the solution.

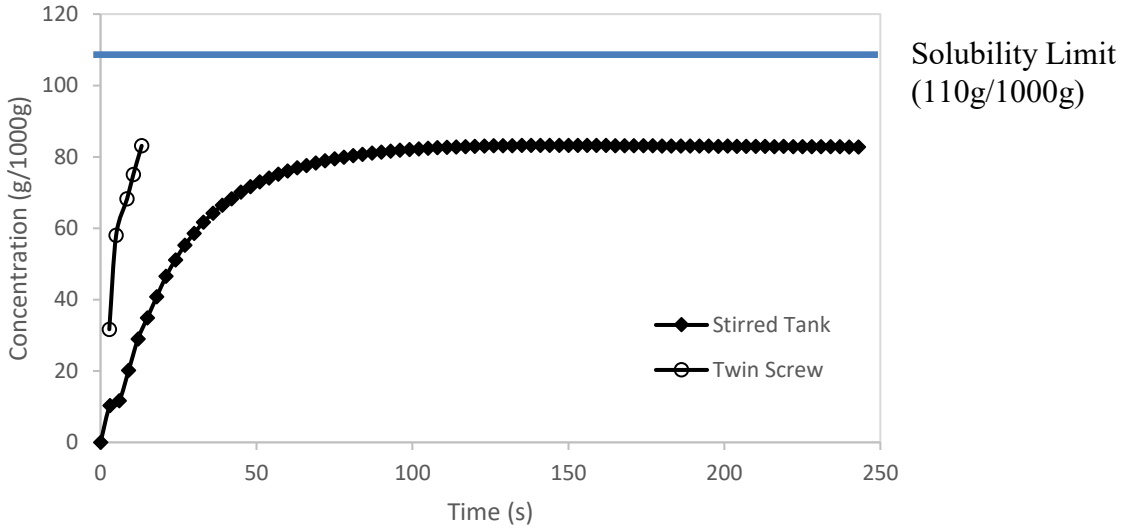


Figure 13 Dissolution profile of granular paracetamol in water/IPA (80:20) at 40˚C according to two methods

Table 6 Dissolution rate constants from a stirred tank vessel and a twin screw extruder

	Dissolution Rate constant, k (s^{-1})	Dissolution rate constant per power density ($m^3\ W^{-1}\ s^{-1}$)
Stirred Tank	0.0175	5.48×10^{-6}
Twin Screw Extruder	0.0441	7.39×10^{-6}

The dissolution rate constants are given in Table 6 for both devices, however power density should be the basis for such a comparison. The power density of stirred tanks is well reported [33, 34] as:

$$\frac{P}{V} = \frac{P_O \rho {N_s}^3 D_S^5}{V_L} \quad (Wm^{-3}) \qquad (1)$$

Where P/V is the power density (W m^{-3}), ρ the fluid density (kg m^{-3} at 40 °C), N_s the speed of the stirrer (rps), D_S the diameter of the stirrer (m), V_L the volume of liquid in the STC (m^3) and P_O the dimensionless power number of the agitator, which was estimated as 2.3 based on data presented by Nienow and Miles [35] for the type of impellor used in our work.

Previous estimations of power density in a twin screw extruder[36, 37] were based on a non-isothermal melt and a non-Newtonian fluid, covering various conditions including melt temperatures, feed rates and scale of equipment. However, the definition of power density from previous work differs from ours in that we estimate the power dissipated into the liquid or power experienced by the liquid, not the power input by the motor as in previous power consumption calculations. By treating the twin screw extruder as a stirred tank working horizontally, we could estimate the power dissipation as follows. The diameter of the stirrer in eq. (1) becomes the diameter of the screw, while the rotational speed remains the same. There is no similar power number for the twin screw, but the helical screw impellor is the closest. In terms of the liquid

volume, only half of the liquid in the TSE is experiencing the effect of shearing imposed by the twin screws at any given time, as the screw pitch is only 45% filled[38].

Applying these values to eq. (1), the power density for the stirred tank and the TSE are 3196 and 5968 W m^{-3} respectively. It is observed that faster dissolution rate is achieved in the TSE however the power density alone is an insufficient descriptor for comparison with the stirred tank. Other factors influencing the dissolution rate include the short mass transfer distances and the efficient shear mixing in the TSE.

Start up and shut down losses encountered in this work were low. It took approximately 90 seconds to reach steady state on starting the equipment from empty which equates to losses of approximately 3 g solid and 50 ml solvent. On shutdown the material remaining in the barrel equates to losses of approximately 1g of solid and 8 ml of solvent.

CONCLUSIONS

In this work, we have demonstrated that the twin screw extruder enables the decoupling of liquid from the solid feed, thus eliminating any potential fouled solid feeding even at low solid feed, e.g. 1.67 g min^{-1}. It also allows the controlled and synchronised input flows, together with intense mixing, to deliver either a dissolved solution or suspension of controlled composition ready for the next unit operation in the process train. These are the novelties of this work, they fill the gap for continuous reaction and crystallisation in the pharmaceutical industry. This study also

highlights the flexibility of the TSE to cope with different raw material feed stocks; achieving full dissolution of powder paracetamol within the residence time of the TSE and achieving full dissolution of granular paracetamol by altering key variables such as solid or liquid feed rates and barrel temperature.

We have, for the first time, proposed an alternative method of estimating the power density for the TSE when used as a continuous dissolution feed stream. This enables a fair comparison of the dissolution rates between two devices, i.e. TSE and stirred tank. The faster dissolution rate in the TSE is associated with higher power dissipation generated by the aggressive shear mixing and thermal energy within the barrel. The dissolution rate constant per power density in the TSE is slightly more favourable than that in the stirred tank. In addition, the variability in the output concentration in the former (1%) is much less than that in the latter (up to 10%)[39] . We are carrying out further tests using a range of diverse materials and will report our results in a separate communication.

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REFERENCES

1. Ni, X., Continuous Oscillatory Baffled Reactor Technology. *Innovations in Pharmaceutical Technology* **2006,** *20*, 90-96.
2. McGlone, T.; Briggs, N. E. B.; Clark, C. A.; Brown, C. J.; Sefcik, J.; Florence, A. J., Oscillatory Flow Reactors (OFRs) for Continuous Manufacturing and Crystallization. *Organic Process Research & Development* **2015,** *19*, 1186-1202.
3. O'Connor, T.; Lee, S., Chapter 37 - Emerging Technology for Modernizing Pharmaceutical Production: Continuous Manufacturing A2 - Qiu, Yihong. In *Developing Solid Oral Dosage Forms (Second Edition)*, Chen, Y.; Zhang, G. G. Z.; Yu, L.; Mantri, R. V., Eds. Academic Press: Boston, 2017; pp 1031-1046.
4. Simon Lawton, G. S., Phil Shering, Continuous Crystallization of Pharmaceuticals Using a Continuous Oscillatory Baffled Crystallizer. *Organic Process Research & Development* **2009,,** *13*, 1357–1363.

5. Ferguson, S.; Morris, G.; Hao, H. X.; Barrett, M.; Glennon, B., Characterization of the anti-solvent batch, plug flow and MSMPR crystallization of benzoic acid. *Chemical Engineering Science* **2013,** *104*, 44-54.
6. Salvatore, M.; L., H. P.; Haitao, Z.; Richard, L.; Brahim, B.; I., B. P.; D., B. R.; L., C. C.; B., E. J. M.; F., J. T.; F., J. K.; S., M. A.; L., T. B., End-to-End Continuous Manufacturing of Pharmaceuticals: Integrated Synthesis, Purification, and Final Dosage Formation. *Angewandte Chemie International Edition* **2013,** *52*, 12359-12363.
7. Bernhard, G.; David, C.; Oliver, K. C., Continuous-Flow Technology—A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angewandte Chemie International Edition* **2015,** *54*, 6688-6728.
8. Besenhard, M. O.; Neugebauer, P.; Scheibelhofer, O.; Khinast, J. G., Crystal Engineering in Continuous Plug-Flow Crystallizers. *Crystal Growth & Design* **2017,** *17*, 6432-6444.
9. Wood, A., Generic Batch Procedures for Flexible Manufacturing. *Control Engineering* **2009,** *56*, P1-P5.

10. Hörmann, T.; Suzzi, D.; Khinast, J. G., Mixing and Dissolution Processes of Pharmaceutical Bulk Materials in Stirred Tanks: Experimental and Numerical Investigations. *Ind. Eng. Chem. Res.* **2011,** *50*, 12011-12025.
11. Paul, E. L.; Midler, M.; Sun, Y., Mixing in the Fine Chemicals and Pharmaceutical Industries. In *Handbook of Industrial Mixing*, John Wiley & Sons, Inc.2004; pp 1027-1069.
12. Atiemo-Obeng, V. A.; Penney, W. R.; Armenante, P., Solid–Liquid Mixing. In *Handbook of Industrial Mixing*, John Wiley & Sons, Inc.2004; pp 543-584.
13. Hemrajani, R. R.; Tatterson, G. B., Mechanically Stirred Vessels. In *Handbook of Industrial Mixing*, John Wiley & Sons, Inc.2004; pp 345-390.
14. Thakur, R. K.; Vial, C.; Nigam, K. D. P.; Nauman, E. B.; Djelveh, G., Static Mixers in the Process Industries—A Review. *Chemical Engineering Research and Design* **2003,** *81*, 787-826.
15. Ghanem, A.; Lemenand, T.; Della Valle, D.; Peerhossaini, H., Static mixers: Mechanisms, applications, and characterization methods – A review. *Chemical Engineering Research and Design* **2014,** *92*, 205-228.
16. Baker, J. R., Motionless mixers stir up new uses. *Chemical Engineering Progress* **1991,** *87*, 32-38.
17. Crowley, M. M.; Zhang, F.; Repka, M. A.; Thumma, S.; Upadhye, S. B.; Battu, S. K.; McGinity, J. W.; Martin, C., Pharmaceutical applications of hot-melt extrusion: part I. *Drug development and industrial pharmacy* **2007,** *33*, 909-26.
18. Repka, M. A.; Battu, S. K.; Upadhye, S. B.; Thumma, S.; Crowley, M. M.; Zhang, F.; Martin, C.; McGinity, J. W., Pharmaceutical applications of hot-melt extrusion: Part II. *Drug development and industrial pharmacy* **2007,** *33*, 1043-57.
19. Patil, H.; Tiwari, R. V.; Repka, M. A., Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation. *AAPS PharmSciTech* **2015**.
20. Martinez-Marcos, L.; Lamprou, D. A.; McBurney, R. T.; Halbert, G. W., A novel hot-melt extrusion formulation of albendazole for increasing dissolution properties. *International journal of pharmaceutics* **2016,** *499*, 175-185.
21. Vercruysse, J.; Córdoba Díaz, D.; Peeters, E.; Fonteyne, M.; Delaet, U.; Van Assche, I.; De Beer, T.; Remon, J. P.; Vervaet, C., Continuous twin screw granulation: Influence of process variables on granule and tablet quality. *European Journal of Pharmaceutics and Biopharmaceutics* **2012,** *82*, 205-211.
22. Mendez Torrecillas, C.; Halbert, G. W.; Lamprou, D. A., A novel methodology to study polymodal particle size distributions produced during continuous wet granulation. *International journal of pharmaceutics* **2017,** *519*, 230-239.
23. Dhenge, R. M.; Cartwright, J. J.; Doughty, D. G.; Hounslow, M. J.; Salman, A. D., Twin screw wet granulation: Effect of powder feed rate. *Advanced Powder Technology* **2011,** *22*, 162-166.
24. Dhenge, R. M.; Cartwright, J. J.; Hounslow, M. J.; Salman, A. D., Twin screw wet granulation: Effects of properties of granulation liquid. *Powder Technology* **2012,** *229*, 126-136.
25. Saleh, M. F.; Dhenge, R. M.; Cartwright, J. J.; Hounslow, M. J.; Salman, A. D., Twin screw wet granulation: Binder delivery. *International journal of pharmaceutics* **2015,** *487*, 124-134.
26. Cartwright, J. J.; Robertson, J.; D'Haene, D.; Burke, M. D.; Hennenkamp, J. R., Twin screw wet granulation: Loss in weight feeding of a poorly flowing active pharmaceutical ingredient. *Powder Technology* **2013,** *238*, 116-121.
27. Wang, Y.; Li, T.; Muzzio, F. J.; Glasser, B. J., Predicting feeder performance based on material flow properties. *Powder Technology* **2017,** *308*, 135-148.

28. William E. Engisch, F. J. M., Method for characterization of loss-in-weight feeder equipment. *Powder Technology* **2012,** *228*, 395–403.
29. Rohani, H. H. a. S., Measurement and Prediction of Solubility of Paracetamol in Water-Isopropanol Solution. Part 1. Measurement and Data Analysis. *Organic Process Research & Development* **2006,** *10*, 1101-1109.
30. McLaughlin, A. M.; Robertson, J.; Ni, X., Material characterisation and parameter effects on bulk solid dissolution rate of paracetamol in a stirred tank vessel using an in situ UV-ATR probe. *International Journal of Engineering Research & Science* **2018,** *4*, 10-20.
31. Tingstad, J. E.; Riegelman, S., Dissolution Rate Studies I: Design and Evaluation of a Continuous Flow Apparatus. *Journal of Pharmaceutical Sciences* **1970,** *59*, 692-696.
32. Thiry, J.; Krier, F.; Evrard, B., A review of pharmaceutical extrusion: critical process parameters and scaling-up. *International journal of pharmaceutics* **2015,** *479*, 227-40.
33. Sinnott, R. K., Equipment Selection, Specification and Design. In *Coulson and Richardson's Chemical Engineering Volume 6 - Chemical Engineering Design*, Third ed.; Sinnott, R. K., Ed. Butterworth-Heinemann: Oxford, 1999; pp 471-473.
34. Garside, J.; Davey, R. J., Invited review secondary contact nucleation: kinetics, growth and scale-up. *Chemical Engineering Communications* **1980,** *4*, 393-424.
35. Nienow, A.; Miles, D., Impellor power numbers in closed vessels. *Ind. Eng. Chem. Process Des. Dev.* **1971,** *10*, 41-43.
36. Meijer, H. E. H.; Elemans, P. H. M., The modeling of continuous mixers. Part I: The corotating twin-screw extruder. *Polymer Engineering & Science* **1988,** *28*, 275-290.
37. Kruijt, P. G. M.; Galaktionov, O. S.; Peters, G. W. M.; Meijer, H. E. H., The Mapping Method for Mixing Optimization. *International Polymer Processing* **2001,** *16*, 161-171.
38. Martin, C., Melt Extrusion. In *Materials, Technology and Drug Product Design*, Repka, M. A. L., N. ; DiNunzio, J., Ed. AAPS Advances in the Pharmaceutical Sciences Series 9: Springer, 2013; pp 47-79.
39. Faanes, A.; Skogestad, S., Buffer Tank Design for Acceptable Control Performance. *Ind. Eng. Chem. Res.* **2003,** *42*, 2198-2208.