Material characterisation and parameter effects on bulk solid dissolution rate of paracetamol in a stirred tank vessel using an in situ UV-ATR probe

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Abstract— *The progress from batch to continuous manufacture of pharmaceuticals has highlighted the requirement for dosing solid feed material directly, efficiently and accurately into continuous flow systems. Solids are currently dissolved in batch vessels before feeding into a flow system. This study focuses on gaining scientific understanding on rate kinetics of solid dissolution and parameters affecting solid dosing in current batch systems as a starting point; the knowledge gained will inform future continuous solid dosing work. Paracetamol was the model compound and the mixtures of water/ IPA the solvent systems. An in situ UV spectrometer was used to quantify the concentration of solute in solution during dissolution. In this paper, we present the dissolution kinetics results from a parametric study of effects of temperature, solvents, mixing and particle sizes on dissolution characteristics in a stirred tank vessel. The dissolution profiles from our system are similar to that of published work, with the fastest kinetics for the micronised particles, albeit problematic when dosing as a single shot. Dissolution rate is increased with increasing temperature, solvent content (solubility), mixing intensity and decreasing particle size.*

Keywords— Dissolution, Solid dosing, Continuous Work up, Batch manufacturing, Continuous Pharmaceutical Manufacture, Stirred tank reactor, UV Spectrometry.

I. INTRODUCTION

Traditionally batch manufacture is used to produce pharmaceutical products from synthesis and work up to reaction and from isolation to tableting. Although the introduction of continuous manufacture and crystallisation into the pharmaceutical industry has been gathering momentum (1, 2), work up technology and inventory in pharmaceutical manufacture still remain batch operation (3); "charging solids into a tank of solvent and leaving it stirred for hours" has been the norm in industrial work up operation (4-6) that are too large to use and too inflexible to change for continuous crystallisation (7, 8). As a result, there has generally been a lack of scientific understanding in terms of solid dissolution, dosing and associated operations in batch processes (9, 10). This is also reflected by the very limited publications in this area, as academic researchers largely regard the work up being a technical problem. With the realization of benefits of consistent crystal properties that continuous crystallisation has brought about (11-13), investigations on continuous work up have been identified as an unmet need, this work is one of the earliest research in this area. The ultimate purpose is to be able to feed solute solid particles and the selected solvent concurrently, accurately and continuously into a plug flow system for unit operations; this would require knowledge and understanding of dissolution kinetics, mechanisms and parameters affecting these. The current work addresses this very subject.

Dissolution research began in 1897 when Noyes and Whitney (14) conducted the first dissolution experiments of two sparingly soluble compounds, benzoic acid and lead chloride; noticed that the rate of dissolution was proportional to the difference between the instantaneous concentration, C at time t, and the saturation solubility Cs. The authors attributed the mechanism of dissolution to a thin diffusion layer which was formed around the solid surface and through which the molecules diffused to the bulk aqueous phase.

Higuchi (15) reviewed the diffusion layer model that considered interfacial transport was the limiting step due to a high activation energy level. Danckwerts (16) proposed an alternative mechanism by constantly renewing macroscopic packets of solvent to reach the solid surface and absorb molecules of solute, delivering them to the solution. In the 1950s the pharmaceutical sciences used the concept of in vitro dissolution when it became clear that the dissolution rate was the limiting step. This led to the development of the basket-stirred-flask United States Pharmacopeia (USP) apparatus 1, as an

official dissolution test kit. Since then the factors affecting the dissolution rates in USP apparatus were studied extensively and the degree of agitation, solubility and the surfaces exposed in the solvent were identified as the important factors in determining dissolution; while temperature was previously identified as a factor in dissolution rate (17) in bulk solids dissolution. All of the above factors will be investigated in this study with paracetamol in water/ IPA as the model system.

The solubility of paracetamol in water- propan-2-ol mixtures was evaluated by Hojjati and Rohani (18) using an ATR-FTIR method, in comparison with measurements taken gravimetrically. The results were in good agreement, which also agrees with data from other literature. Granberg and Rasmuson (19) used a gravimetric technique to determine the solubilities of paracetamol in 26 different pure solvents including propan-2-ol and water over the temperature range from -5 to +30°C. Fujiwara et al (20) measured the solubility of paracetamol in water from 20 to 50°C using in situ ATR-FTIR probe and chemometric techniques. The agreement among the aforementioned solubilities was good. The solubility data for paracetamol in water- propan-2-ol mixtures (18) is used in this study and verified using a gravimetric technique.

While solubility was measured and reported in previous research work, dissolution kinetics were largely ignored, but it is the kinetics that governs the dissolution process. This work focuses on a parametric study of the effects of temperature, solvent composition, mixing intensity and particle size on dissolution rates in a stirred tank vessel (STV). Solute concentration was measured using an in situ ATR-UV probe, were extracted to obtain dissolution kinetics. This work serves as a baseline for developing dissolution of solids in a continuous flow system.

II. EXPERIMENTAL PREPARATION AND PROCEDURES

2.1 Materials

Three grades (micronised, powder and granular) of paracetamol (99% purity) were supplied by Mallinckrodt Chemical Limited (UK). Table 1 shows the characteristics of the three grades.

TABLE 1
PARTICLE SIZES OF THREE TYPES OF PARACETAMOL

	40 Mesh (425µm)	60 Mesh (250µm)	80 Mesh (180µm)	100 Mesh (150µm)	400 Mesh (38µm)
Micronised				99% min	95% min
Powder	1% max	7% max		5% - 19%	
Granular	1% max	64% min	10% max		

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

2.2 Solubility Measurement

Three different solvent systems were used in this study: 100% deionised water, 80% deionised water: 20% IPA, and 20% deionised water: 80% IPA. Solubility of paracetamol has been determined by a gravimetric method and compared to previously published work (18). In the gravimetric technique, a known weight of paracetamol was added to a conical flask containing 100g of solvent mixture. The flask was placed in a water bath to maintain the temperature and stirred until all solids had dissolved. Further known weights of paracetamol were added until no further dissolution had occurred. The excess solid was filtered off, dried and weighed to determine the saturation concentration. Each measurement was repeated three times.

2.3 Particle Size Analysis

The mean particle size and particle size distributions were analysed by a Mastersizer 3000™ (HYDRO, Malvern) device and given in Table 2 and Figure 1.

TABLE 2
PARTICLE SIZE DISTRIBUTION OF THREE TYPES OF PARACETAMOL

	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)
Micronised	11	26.1	51.4
Powder	12.6	44.9	124
Granular	263	374	516

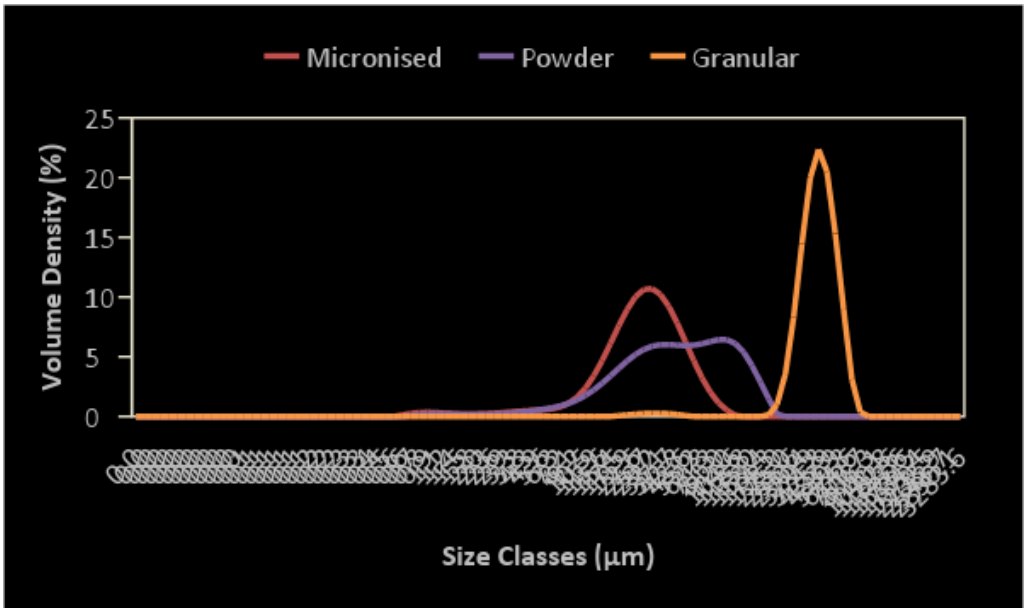

FIGURE 1: PARTICLE SIZE DISTRIBUTION OF PARACETAMOL - MICRONISED, POWDER, GRANULAR

Scanning Electron Microscope (SEM) images (provided by Remedies Project) for each grade of paracetamol are given in Figure 2.

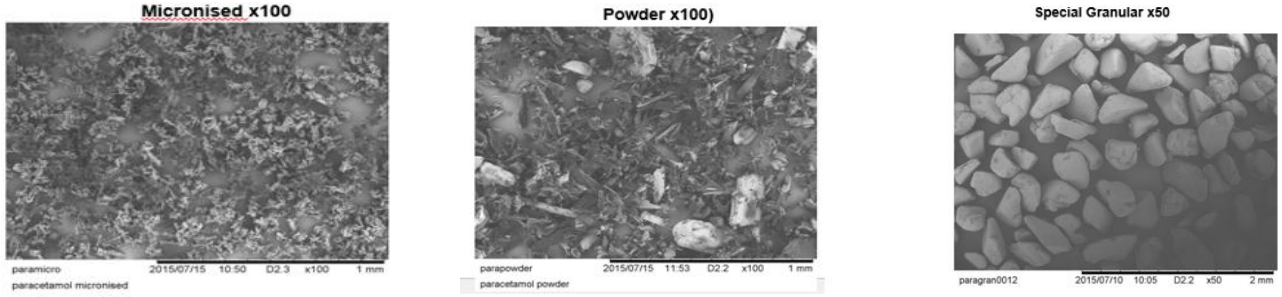

FIGURE 2: SEM IMAGES OF PARACETAMOL MICRONISED PARTICLES, POWDER AND GRANULAR

2.4 Surface area

SMS-iGC 2000 from Surface Measurement Systems Ltd was used to measure the surface area and surface energy of each of the paracetamol grades. Approximately 1 g of each sample was packed by gentle tapping into a 4 mm ID silanised glass column capped with glass wool in each end. Samples were pre-conditioned at 25°C and 0% RH for 1 hour under flowing helium prior to measurements. BET surface area was determined using octane as the vapour probe. The Dorris-Gray calculation method (21) and the peak centre of mass were used to analyse iGC- SEA results to identify the wettability, hydrophilicity and surface energy.

2.5 STV

The STV was a jacketed glass vessel of 1 litre in volume, with a PTFE four-blade pitched impeller to generate mixing. The impeller was attached to an overhead motor to control the rotation speeds. The vessel was fitted with a 5 port PTFE lid which enables the insertion of PAT probes and the dosing funnels. Different temperatures within the vessel were achieved by controlling the jacket temperature using a water bath (Grant Instruments GP 200/R2). UV-ATR, turbidity and temperature (PT100) probes (CrystalEyes system from HEL, UK) were inserted into the vessel to monitor and record the solute concentration, the cloudiness and temperatures of the solution during dissolution. The system was interfaced with a Carl Zeiss MC600 Spectrometer and PC for real-time display, logging and data analysis. The UV spectra were collected continuously over the spectral range of 220 – 280nm, using Aspect Plus software. The schematic illustration of the STV is given in Figure 3.

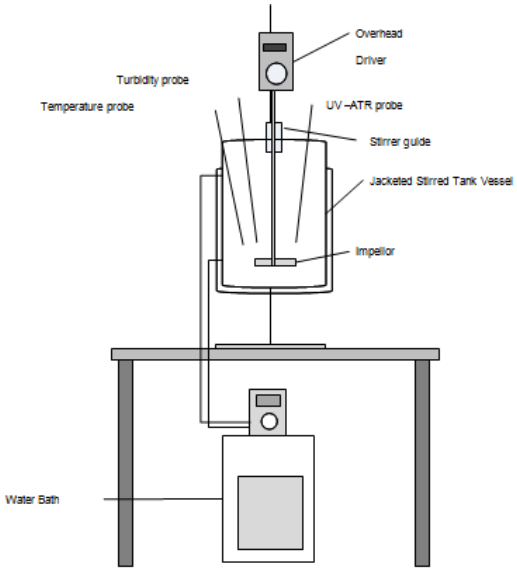

FIGURE 3: SCHEMATIC ILLUSTRATION OF STV SET-UP

For each experimental run, the volume of one litre of solvent was added to the STV and heated/cooled to the desired temperature (20°C, 30°C, or 40°C). The dissolution was carried out isothermally. A specified amount (see Supplementary Material) of technical grade paracetamol was weighed using an electronic balance and was poured into the vessel using a funnel, to minimise loss. It was decided to use a solid loading of 95% of the solubility, in order to obtain an undersaturated solution. The solution was held at temperature and stirred under a fixed rotational speed until dissolution was complete. Dissolution experiments were carried out to determine the parameter effects of temperature (20 ˚C, 30 ˚C, 40 ˚C), mixing intensity (250rpm, 500rpm, 750rpm), solvent composition (water/ IPA mixtures), and particle size (micronised, powder, granular) on the dissolution rate.

III. RESULTS AND DISCUSSION

3.1 Dissolution Studies in STV

3.1.1 Calibration for concentration measurement

To quantify the solute concentration in the solution, calibration graphs were generated from known quantities of paracetamol in solvents based on the Beer's Law where a linear relationship is obeyed between the absorbance and the concentration of an absorbing species. A maximum absorbance peak can be seen at 247nm (for deionised water) indicating that the paracetamol has dissolved (see Figure 4). Calibration curves were generated for each solvent system at each temperature in this parametric study. The data show that the temperature dependence of UV spectra is weak in the range of experimental temperatures. This indicates that temperature should not significantly influence solution concentration measurement which supports previously published work by Zhang et.al. (22). Once the calibration curve has been established, each individual sample can be analysed.

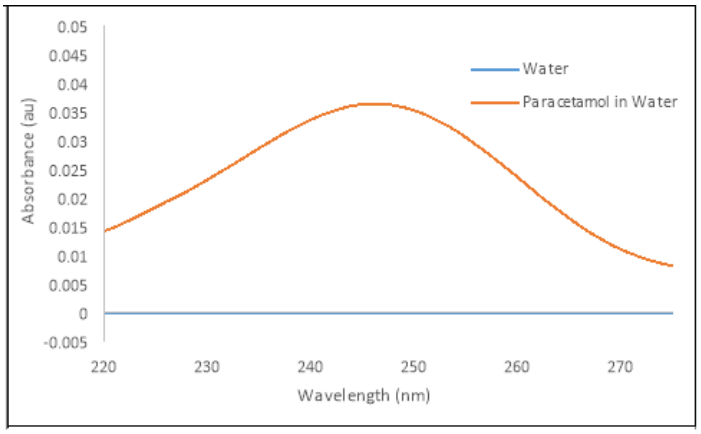

FIGURE 4 UV SPECTROSCOPY OF PARACETAMOL DISSOLUTION IN WATER

3.1.2 Dissolution Kinetics

The dissolution rate kinetics were evaluated by the slopes of the plot of concentration of dissolved paracetamol as a function of time as shown in Figure 5. We see that the slope (i.e. the rate) is relatively steep initially and then levels off monotonously as t increases (see Figure 5). This is the typical behaviour of solid particles whose size and surface area gradually decrease as dissolution proceeds which is called the attrition mechanism (23). The curve flattens off as we are running out of material and dissolution is complete. Under highly under saturated conditions, all dissolution surface sites actively participate in the dissolution reaction, while it is only certain faces of the materials with lower activation energies of dissolution that contribute to the dissolution process as the solution becomes more saturated, as demonstrated by Guidry and Mackenzie (24) for alkali feldspars.

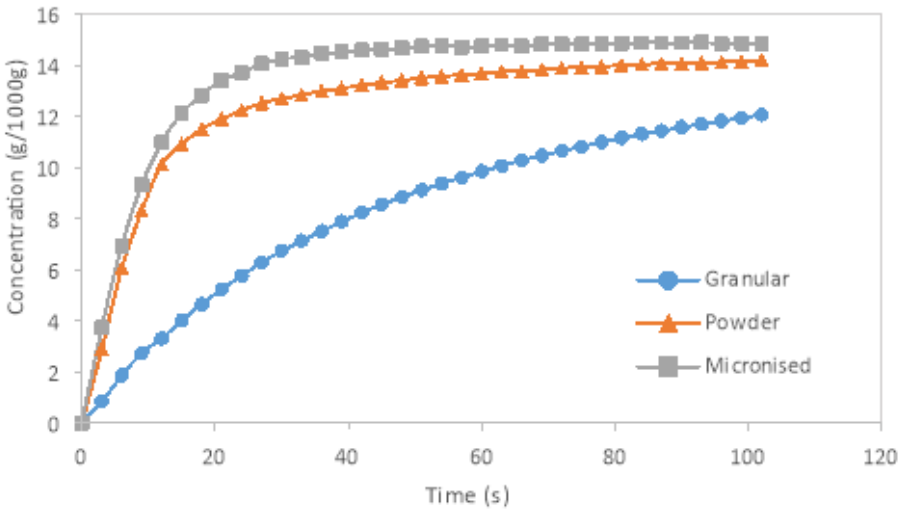

FIGURE 5: DISSOLUTION PROFILE OF PARACETAMOL IN WATER (Temperature = 30°C, Mixing Speed = 750 rpm)

For comparative purposes, the maximum dissolutions observed at the initial dissolution times, i.e. only the rising parts of the dissolution profiles, were used to extract dissolution kinetics, as

$$dC/dt = k(Cs - C)$$

where C is the concentration of paracetamol (g/1000g) at the dissolution time t, Cs is the saturation concentration of paracetamol (g/1000g) and k is the rate constant of dissolution (14).

3.2 Effect of Particle Size

Figure 6 shows the dissolution profiles for the three materials in water at a fixed temperature; for comparison purposes, the time taken to dissolve 90% of the paracetamol concentration was used for each experiment. The granular material took 201 seconds to dissolve and was the slowest; the powder dissolved faster than the granular particles, taking 45 seconds, although the dissolution slowed considerably at near equilibrium concentrations. The micronised material dissolved very fast where a full dissolution was obtained within 21 seconds.

Note that both the micronised and powder particles were difficult to dose due to static force and prone to stick to the walls of the dispensing funnel and sides of the vessel when dispensing in one shot, while dosing granular material was trouble free without loss of material, as such the total concentration of paracetamol dissolved was slightly less for micronised and powder than for granular particles, e.g. 15.6 g l^{-1} (granular), 14.8 g l^{-1} (powder) and 14.8 g l^{-1} (micronised). The data has therefore been normalised (see Figure 6) prior to analysis of the dissolution kinetics.

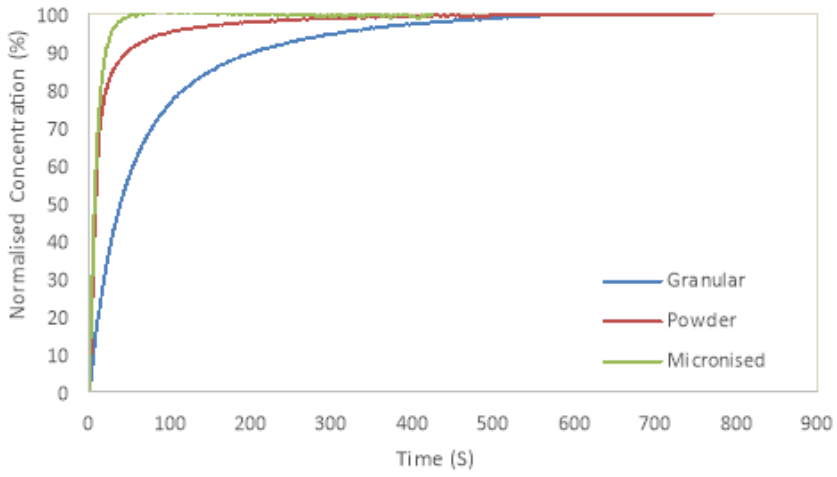

FIGURE 6 NORMALISED DATA FOR DISSOLUTION PROFILE OF PARACETAMOL IN WATER (Temperature = 30°C, Mixing Speed = 750 rpm)

First order kinetics can be seen in Figure 7 and summarised in Table 3, which agrees with previously published work by Lee T. et.al, 2013 (25).

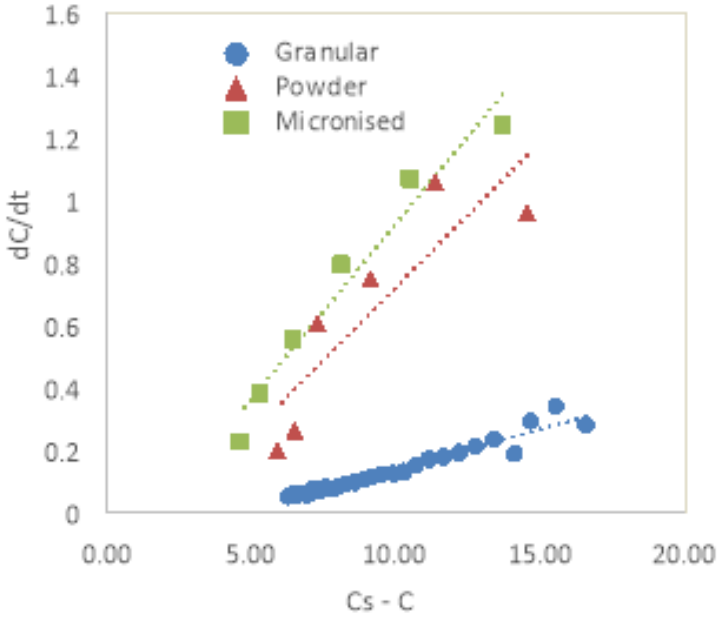

FIGURE 7: KINETIC EVALUATION

TABLE 3
DISSOLUTION RATE CONSTANTS OF PARACETAMOL

Particle Size	k (s^{-1})
Granular	0.026
Powder	0.093
Micronised	0.112

The results from our system are similar to that of literature (25), with the steepest slope for the smallest particles.

3.3 Effect of Solvent Composition

The dissolution profiles for the three solvent systems as a function of time are illustrated in Figure 8 for granular paracetamol only.

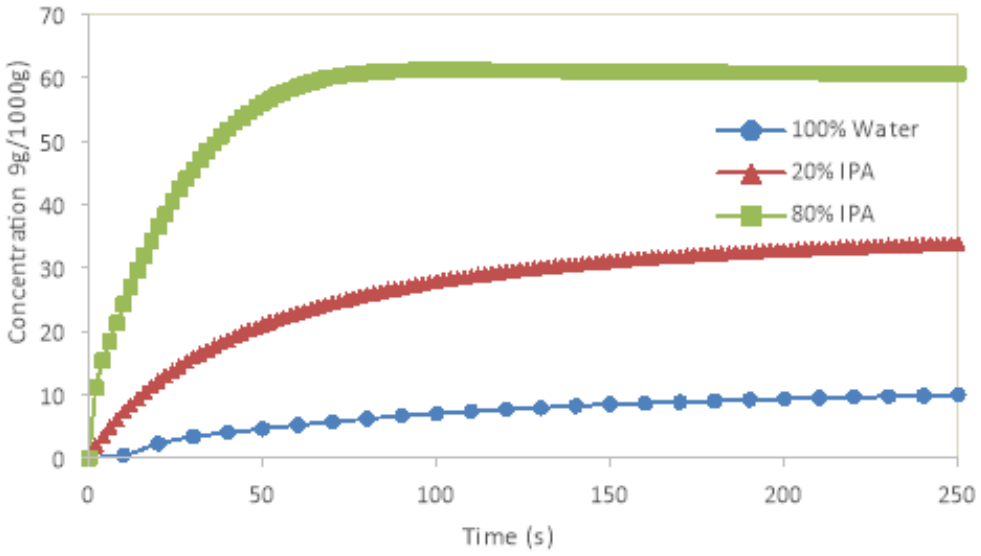

FIGURE 8 DISSOLUTION PROFILE OF GRANULAR PARACETAMOL IN WATER/IPA MIXTURES (Temp=20°C, Mixing Speed = 750 rpm)

The higher the IPA content and hence the higher the solubility, then the faster the dissolution rate, as highlighted in Table 4.

TABLE 4
TIME TO DISSOLUTION OF GRANULAR PARACETAMOL IN VARYING SOLVENT COMPOSITIONS

	Dissolution Time (s)
100% Water	440
20% IPA	18
80% IPA	2

Paracetamol has a simple molecular structure showing polar property. Barra and et al, (27) studied the hydrogen bonding ability of paracetamol as a donor and an acceptor. Water is very polar, while IPA is less polar; lower polarity of IPA reduces the interfacial tensions and surface tension between the solute and solvent; the solute moves faster through the diffusion layer of the solvent, hence increasing the dissolution rate (see Table 5).

TABLE 5
DISSOLUTION RATE CONSTANTS FOR WATER/IPA MIXTURES

Solvent Composition	k (s^{-1})
100% Water	0.01
Water/IPA (80:20)	0.06
Water/IPA (20:80)	0.79

Solvent composition comprises of varying the solubility of the system by altering the amount of IPA used in water. The magnitude of the solubility gives some clues about the mode (transport or surface reaction) that controls the dissolution rate of the solid. Lasaga (26) stated that for aqueous solutions, solids with low solubility dissolve by surface control, whereas highly soluble solutes dissolve by transport control. These mechanisms are applicable to our case. In short, solvent composition is a major factor affecting dissolution rate of solute molecules for a given particle type.

3.4 Effect of Temperature

The temperature effects were studied at three different temperatures (20°C, 30°C, and 40°C) for granular paracetamol particles in water. Increasing the temperature of the solvent increases the solubility of the drug and hence increases the dissolution rate as shown in Figure 9.

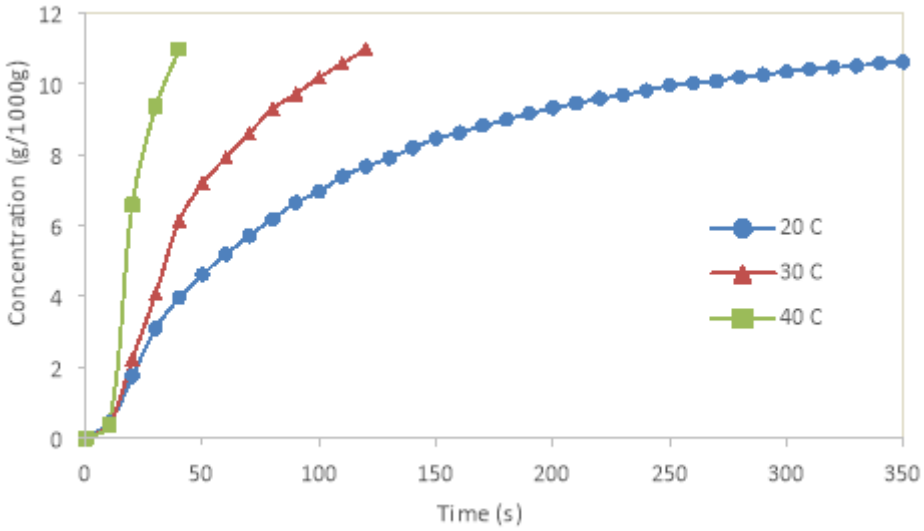

FIGURE 9 DISSOLUTION PROFILE OF GRANULAR PARACETAMOL IN WATER (MIXING SPEED = 500 RPM)

The dissolution rate constant obeys the Arrhenius equation, higher temperatures results in an increase in the rate constant (see Table 6).

TABLE 6
DISSOLUTION RATE CONSTANTS AT VARYING TEMPERATURES

Temperature	k (s^{-1})
20°C	0.01
30°C	0.03
40°C	0.09

The dissolution rate is approximately 3 times faster for every 10 degree rise in temperature which is consistent with the reduction in dissolution time by approximately 1/3 for each 10 degree increase as shown in Table 7.

TABLE 7
TIME TO DISSOLUTION OF GRANULAR PARACETAMOL IN VARYING SOLVENT COMPOSITIONS

	Dissolution Time (s)
20°C	350
30°C	100
40°C	30

Using a pair of temperatures and rate constants in Table 6, the activation energy (and the frequency factor) can be calculated for this dissolution as 19.45 kJ mol^{-1}. Sparks (28) indicated that typical values of activation energies <21 kJ mol^{-1} were for transport-controlled processes in water and 42–84 kJ mol^{-1} for surface reaction controlled at solid surfaces. It must be noted that these values were established for dissolution of minerals, and may not apply strictly to the dissolution of paracetamol particles. Nevertheless, the low value of activation energy (19.45 kJ mol^{-1}) deduced from Figure 9 indicates that paracetamol dissolution is controlled by transport processes in water.

3.5 Effect of Mixing Intensity

The intensity of the mixing was varied by increasing the agitator speed (250 rpm, 500 rpm, and 750 rpm) for dissolution of powder paracetamol particles in water at 20 ^{o}C. The impact of increasing the mixing within the STV resulted in increased dissolution rate as shown in Figure 10.

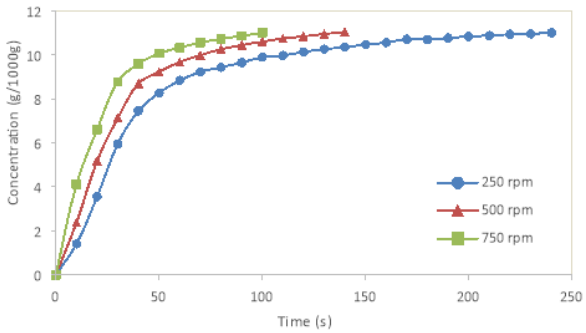

FIGURE 10 DISSOLUTION PROFILE OF PARACETAMOL POWDER IN WATER (Temperature = 20°C)

At increased mixing intensity the solvent/solute boundary layer is replenished faster with fresh solvent increasing diffusion of solute into the solvent and therefore increases the dissolution rate (see Table 8).

TABLE 8
DISSOLUTION RATE CONSTANTS AT VARYING MIXING INTENSITIES

Agitator Speed	$^{k}(s^{-1})$
250 rpm	0.022
500 rpm	0.034
750 rpm	0.059

While the dissolution rate constant increases linearly with the stirring rate (r^2 = 0.995), the overall effect of mixing intensity on dissolution is much less than either that of temperature or solvent composition.

IV. CONCLUSION

Some critical factors impacting the dissolution rate in a batch system are realised through this initial study. For the same type of particles, solvent composition (solubility) is the major parameter when dissolving bulk solids in a batch system, temperature is the 2nd contributing factor, while mixing has less effect on dissolution rates. For the same solvent and temperature, the smallest particle size has the fastest dissolution rate. The mechanism for dissolution of paracetamol in the stirred tank vessel could be the combination of both surface and transport processes. Although micronised solids increased the dissolution rate, the flowability of such material would have a negative impact in a continuous flow system, potentially leading to bridging, blockages for instance. The learning from this work is being applied to the investigation of solid dissolution in a continuous flow system using a twin screw mixer. We shall report these in a separate communication.

ACKNOWLEDGEMENTS

Authors would like to thank EPSRC, the Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation, and GSK for their support and funding. Particular thanks and acknowledgement goes to the mentoring support provided by Gareth Alford, GSK. The helpful discussions with Deborah Bowering, University of Strathclyde is also acknowledged. The authors would like to acknowledge that this work was carried out in the CMAC National Facility, housed within the University of Strathclyde's Technology and Innovation Centre, and funded with a UKRPIF (UK Research Partnership Institute Fund) capital award, SFC ref. H13054, from the Higher Education Funding Council for England (HEFCE).

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SUPPLEMENTARY MATERIAL

TABLE 1
COMPARISON OF MEASURED SOLUBILITY USING GRAVIMETRIC TECHNIQUE AND REPORTED SOLUBILITY USING ATR-FTIR TECHNIQUE FOR PARACETAMOL IN WATER – IPA MIXTURES

Water Mass (%)	T (°C)	Measured Solubility (g/1000g solvent)	Reported Solubility (g/1000g solvent)	% Error
20	20	218.60	224.95	2.8
20	30	264.34	274.01	3.5
20	40	321.83	331.72	3.0
80	20	43.96	45.69	3.8
80	30	68.64	70.45	2.6
80	40	103.90	107.67	3.5
100	20	11.91	12.22	2.5
100	30	17.21	17.36	0.9
100	40	24.21	24.75	2.2

TABLE 2
SOLID LOADING OF PARACETAMOL

Solid Loading (g/l)			
Solvent System	**20˚C**	**30˚C**	**40˚C**
Water	11.61	16.49	23.51
Water/IPA (80:20)	43.41	66.93	102.29
Water/IPA (20:80)	213.70	260.31	315.13