Development of a continuous evaporation system for an API solution stream prior to crystallization

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1.0 Abstract

A bubble column was investigated as a method to achieve a desired and controllable rate of evaporation of a pharmaceutical solution. Applying a thermodynamic model to predict the rate of evaporation, all predicted values were observed to have accuracies within the bounds of instrumentation errors (<5% absolute). The thermodynamic model accounted for the measured effect of reduced vapor pressure caused by the dissolved solids as a function of their concentration. A general method to obtain accurate measurement of this effect is introduced and applied, improving the accuracy of model predictions. Predicting the rate of evaporation using the developed model, consistent and repeatable evaporation rates ranging from 0.7 – 6.9 g/min were achieved, and errors between predicted rates and experimental ranged from 0.219% to 4.19% absolute. This demonstrates a more controllable and flexible alternative to the evaporation of process streams compared to boiling. The column was configured in a continuous mode and coupled to a downstream crystallizer (MSMPR). Using the column as a controllable concentrator, the concentration of a dilute feed stream of paracetamol in methanol was increased in a single equilibrium stage. The column demonstrated the ability to concentrate the solution in flow by 179%, delivering an output of 2mL/min to the MSMPR. The MSMPR achieved steady-state of control, measured by offline dissolved concentration analysis and particle count by FBRM in situ, highlighting the potential of the column to perform reliably in continuous tandem.

2.0 Introduction

In recent years, the benefits of adapting to Continuous Manufacturing (CM) for the production of pharmaceuticals and fine chemicals have been highlighted by reported improvements in several key aspects such as improved process safety, reduced footprint and waste production, improved overall heat & mass transfer efficiencies, and process chain flexibility (Lee, et al., 2015; Wood, et al., 2019; Escribà-Gelonch, et al., 2018; O'Mahony, et al., 2017; May, et al., 2016; Power, et al., 2015; Plumb, 2005). As CM becomes a more established method within the industry the demand for more configurable and controllable unit operations grows while engineers continue to reduce overall process footprints (Cole, et al., 2017). The inherent nature of CM allows for the processing of aligned unit operations at both lab and pilot scale, offering the flexibility for faster reconfiguration and throughput modification of the process to meet fluctuating market demands. Conventional batch equipment such as large batch reactors, crystallizers and mixer-settlers are replaced by smaller scale plug flow reactors (PFRs), mixed-suspension mixed-product-removal crystallisers (MSMPRs), and liquid-liquid separators, reducing footprint and enhancing process economies (Power, et al., 2015; Roche, et al., 2020; Diab & Gerogiorgis, 2019).

Bubble columns have been shown to offer high rates of mass and heat transfer throughout, due to the intimate contact of the two phases and the enhanced mixing profiles provided by the bubble dynamics (Donnellan, et al., 2015; Donnellan, et al., 2014; Kulkarni & Joshi, 2011; Lage & Campos, 2004; Kantarci, et al., 2005). Also advantageous is their relative simplicity of installation, requiring no moving parts and easily introduced in most working fume hoods with suitable plumbing. Here, it is proposed that they may provide a suitable alternative to conventional evaporation operations such as large scale boilers, providing typical production

CM scale rates of evaporation, which can be often less than 1g/min (Hartman, et al., 2010; Deadman, et al., 2013; Taseidifar, et al., 2018).

Over the previous decade, bubble columns have been applied to achieve evaporation of salt water for desalination and to obtain accurate thermodynamic properties such as the enthalpy of vaporisation of pure water and of electrolyte solutions of known concentrations (Shahid & Pashley, 2014). Although not the goal of these studies, such published work highlight the bubble column's capacity to achieve appreciable vaporisation rates of aqueous solutions with relatively simple installation and low equipment footprint. An economic study carried out by Shahid et al (Shahid, et al., 2016) heated the gas to high temperatures in-line prior to introduction to the column (150-275°C), achieving rates of up to 2.64g/min of water evaporation at gas inlets of up to 21L/min at steady-state solution temperatures lower than 55°C.

Recycled gaseous waste streams have been investigated as a method of achieving economical evaporation in a bubble column, bringing about the term Direct Contact Evaporators (DCEs) when they're employed in this configuration (Ribeiro Jr & Lage, 2004; Shahid, et al., 2016). The inert, high-temperature gaseous waste streams enter the columns, typically through a sintered frit or designed sparger, and are dispersed throughout the solution to be concentrated. This produces high rates of heat and mass transfer and causes vaporization of the continuous phase which is often a caustic aqueous solution. A compiled review (Ribeiro & Lage, 2005) describes achieved rates of evaporation of water and various solutions, ranging from 0.67 – 3249 g min^{-1} at process temperatures ranging from 57-102°C and column diameters ranging from 6 – 91.4cm. Although the flow rates of waste gaseous streams are not discussed, the thermal efficiency value is described to consistently achieve

above 80%, independent of the properties of the continuous or dispersed phases. This range of evaporation rates is attractive for application in CM of pharmaceuticals, demonstrating appreciable evaporation rates at temperatures 20-40°C lower than the typical boiling points of solvents. Although APIs may show resistance to thermal deterioration, they are often maintained at lower temperatures during processing when stability data is unavailable. This is often the case for products at the clinical stage of manufacturing, where stability data is minimal. Maintaining low temperature processing has the benefit of reducing the likelihood of localized hotspots forming, as is often the case with conventional evaporation equipment.

The work referenced previously all describe a thermally uncontrolled system, in which the heat is added to the system solely by the gaseous stream entering the control volume, eventually reaching an equilibrium. Inaba et al (Inaba, et al., 2002) however maintained the solution temperature at a desired value via circulation through an external heat exchanger while the gas streams were introduced at room temperature. The heat and mass transfer achieved was equivalent to that of the high temperature gas studies previously referenced, and although it was not the goal of the work, an equal rate of vaporization was also achieved, as described by the measured humidity of the outlet streams at the known gas flow rates (7.8-37.8 L min^{-1} in a 100mm diameter rectangular column).

Previously (Roche, et al., 2020) a study was performed in a thermally controlled bubble column to assess the achievable rates of evaporation of pharmaceutical solutions, in batch and continuous configurations. Building on this work, a bubble column is applied here in a similar configuration as an evaporation unit operation for solutions containing a pharmaceutical API. The column achieves a more concentrated solution in a fully continuous fashion (i.e. without breaking the process chain), while predicting the rate of vaporization. A

further assessment of the bubble column capacity is also carried out, by increasing the throughput of the column operating as a single equilibrium stage.

For this work, gas is introduced to a bubble column at room temperature and known flow rates with the solution temperature controlled by an external jacket. Methanol and paracetamol were chosen as a case study for this work, due to their well-developed solubility profiles, minimising the risk of undesired precipitation during concentration experiments (Granberg & Rasmuson, 1999). This work draws a focus on achieving accurate and controllable evaporation rates, by building on the thermodynamic model developed previously by (Roche, et al., 2020). This is achieved by accounting for the reduction on evaporation rate imposed by the increasing dissolved solute concentration. To this author's best knowledge, a highly predictable and controllable method for continuous, low temperature evaporation of pharmaceutical solutions is yet to be published in the literature.

Various experiments are performed to assess the throughput capacity and achievable evaporation rates of the column to perform as a solution concentrator, in batch and continuous mode configurations. Lastly, it was desired to simulate a segment of a typical continuous process chain where concentration of the solution is required. The transfer from a relatively dilute reaction stream to an MSMPR is selected, where a higher solute concentration is required in the crystalliser to enable sufficient yields of solids.

3.0 Experimental Method

3.1 Bubble Column Evaporator

All experiments were performed using a jacketed, cylindrical, glass bubble column of 3cm inner diameter and 40cm in height (Figure 1). Dry air from a house supply (regulated at 3bar) was fed to the base of the column at a known rate using a needle valve and variable-

area rotameter (Omega Engineering FL-2013, 0.4-5LPM ±250mL accuracy). All gas flowrates were also confirmed by water displacement experiments before each experiment. The gas passed through a sintered frit (40-100µm pore diameter), dispersing evenly into the liquid. The temperature of the solution was controlled by passing a heated fluid (50:50 propylene glycol and water solution) through the annular external jacket of the column using a Julabo F34-HE circulation unit, set to a desired temperature.

The process temperature was measured using a thermocouple (RS Pro Type K) and digital thermometer (RS Pro Digital Thermometer, ±0.3% accuracy) at the vapour outlet of the column. The feed solution was heated to a desired temperature using a stirred hot-plate (Yellow Line, Yellow Mag HS 7, ±0.5°C control accuracy) with an immersed thermocouple control loop (PT-1000).

The flowrate of the liquid solution to the column was controlled using a peristaltic pump (Cole Palmer Masterflex L/S Digital Pump & Easy-Load©II Pump Head; ¼" PTFE Tubing, Masterflex 77390-series), which was calibrated before each experiment to deliver a consistent supply of solution from the feed tank. Each run was started with a 'dry column' (i.e.: containing no solution) with the desired gas flowrate and jacket temperature set before introducing liquid flow. This approach was selected to enable steady state operation conditions to be reached faster, as described in section 5.5. For the outlet flow, a dip-pipe was applied at a fixed, vertical position within the column. A second peristaltic pump removed the fluid from the column at a rate high enough to maintain the solution volume at a constant level during operation.

The mass flowrates of the streams were calibrated gravimetrically using a balance (Mettler Toledo XS6002S, Linearity ±20mg) with an RS-232 digital output to log the mass of removed

from the feed tank over time. A Py-Serial Python script, giving 2 readings per second from the balance, was used to collate the RS-232 output from the mass balance, allowing the slope of the linear profile to be interpreted as the mass flow rate. Once the pumps were calibrated, the same balance could then be configured at the outlet to record the rate of accumulation of the exiting stream over time.

Samples of the solution were taken at discrete time points throughout each experiment and their respective concentrations were measured offline, both gravimetrically and using gas chromatography (Shimadzu Nexis GC-2030). For the gravimetric samples, weights were measured as a sealed solution (to prevent losses) and subsequently dried in a vacuum oven to obtain the dry residue. For gas chromatography, the concentration of paracetamol in methanol solution samples was measured relative to a known amount of internal standard (2-butanone), and compared to a previously developed response factor calibration curve, following the method of Grob & Kaiser (Grob & Kaiser, 2004)

3.2 MSMPR Operation

The ability to couple and chain numerous unit operations is a very important factor underpinning many of the advantages of CM and gives rise to the flexibility regarding overall process design. In this work, it is intended to couple the bubble column evaporator with a downstream mixed suspension, mixed product removal crystallizer (MSMPR) to achieve crystalline product continuously from a dilute feed stream. MSMPRs are one of the most commonly encountered units selected for continuous crystallization due to their relative simplicity and lower tendency to cause blockages compared to a plug flow units (Wood, et al., 2019). It is intended to utilise the upstream bubble column evaporator to improve the

theoretical yield of a crystallization process by increasing the concentration of the solution entering the MSMPR.

To design the overall process, it was necessary to initially design the MSMPR's desired residence time throughput. An Easymax (Mettler Toledo) with a working volume of 80mL was used as the crystallization vessel, and its temperature was held constant at -5°C. This provided a mother liquor saturation concentration of 0.1745 g/g (0.827 M) of paracetamol in methanol (Granberg & Rasmuson, 1999). The solubility of paracetamol in methanol is very high and an appreciable amount of solute remains dissolved in the mother liquor following crystallisation; however the objective of this work is to successfully connect the units in tandem to ascertain a steady state operating condition, and hence optimisation of the crystallisation itself is considered beyond the scope of this work.

The MSMPR (Mettler Toledo Easymax 102, Figure 1) was designed to operate with a working volume of 80mL in a 100mL glass reactor, with a C-22 Hastelloy stirrer of 45° pitch. The agitation rate was maintained at 350RPM for all experiments, while the temperature was controlled using iControl 5.5 (Mettler Toledo Software), and measured using the associated PT100 probe. A dip tube inserted into the crystallizer at a desired height allowed the liquid volume to be controlled by removing a volume of suspended slurry at high velocities with periodic headspace nitrogen pressurization, following a method as described in the literature (Power, et al., 2015; Hou, et al., 2014). The nitrogen was purged through this system for a duration to ensure a full slurry transfer and prevent encrustation within the transfer lines. The periodic control of the nitrogen headspace pressurization was performed using a set of timed, automated solenoid valves and an associated programmable software.

The continuous process was initiated from a completed batch crystallization system, to facilitate reaching steady-state conditions in shorter time due to the self-nucleating effect of the initial crystals (Wood, et al., 2019).

The MSMPR was designed to operate with a residence time of 40 minutes and the crystallization process performance was monitored using an FBRM (Mettler Toledo Particletrack G400) for obtaining the in-situ count of chord lengths. The probe was positioned next to the agitator in the expected flow direction of the dispersed solids; this was to provide an optimum continuous sample to the probe window while minimising the potential of fouling (Barrett & Glennon, 1999).

The solution leaving the bubble column entered the MSMPR directly and underwent cooling crystallisation. Steady state operation was determined by analysis of the dissolved concentration of the mother liquor by taking offline, filtered samples at discrete time points, and by FBRM trending of the overall particle counts. Both gravimetric and gas chromatography analysis of concentration was conducted for all samples.

3.3 Measurement of Reduced Vapour Pressure

This work is a modification of the study by Chen et al (Chen, et al., 2016), using an isoteniscope to measure the vapour pressure of a concentrated solution and to analyse the impact dissolved solids have on the system. The device and associated rotavapor configuration are illustrated in Figure 3a and Figure 3b. The device consists of an enclosed chamber which is intended to hold a volume (~40mL) of the process fluid, at a known temperature, whose vapour pressure is to be measured. Further details on the method are available in the SI.

Due to an initially applied vacuum on the system, the force exerted upon the solution in the U-bend on the chamber side can be assumed to be entirely contributed by the pressure exerted by the solution vapour in its purity. This was recognised to be the solution's characteristic saturation vapour pressure, a function of temperature and its concentration. The temperature was increased as desired and the experiment repeated to build the profiles as shown in Figure 4 and Figure 5.

A range of concentrations spanning from purity to 1M was analysed for the effect of vapour pressure reduction. The Antoine Equation was applied to each experimentally obtained data set and a least squares regression was applied to obtain new constants that gave a good fit for the concentration profiles. Table 1 shows the Normalised Root Mean Square Deviation (NRMSD) of the data fits from the modified Antoine Equation to the experimental data as a percentage. (Sample equation in the SI)

4.0 Mathematical Modelling

4.1 Modelling the Rate of Evaporation

A model is developed to accompany the experimental work in this study, which predicts the rate of evaporation of a continuous stream of solvent containing dissolved API using dry air as the mass-transfer driving force. Previously published work by Roche et al (Roche, et al., 2020) describes the rate of solvent evaporation within a bubble column for a known gas flow rate and temperature:

$$\frac{dm}{dt} = \frac{Q_{air} . M_w . \frac{P^{SAT}}{R . T}\left[1 - \exp\left(-k_v a . t_{res}\right)\right]}{1 - \frac{M_w . \frac{P^{SAT}}{R . T}\left[1 - \exp\left(-k_v a . t_{res}\right)\right]}{\rho_v}} \quad (1.0)$$

where *dm/dt* is the rate of evaporation of liquid (kg/s); *Q* is the flow rate of gas into the column (m^3/s); M_W the molecular weight of the liquid to be evaporated (kg/mol); P^{SAT} the saturation vapour pressure of the liquid solution (Pa); *T* the temperature of the vapour phase leaving the column (K); $k_v a$ the gas-side volumetric mass transfer coefficient (s^{-1}); t_{res} the bubble residence time in contact with the liquid (s); ρ_v the density of the vapour leaving the column (kg/m^3).

It was demonstrated by Roche et al (Roche, et al., 2020) that the gas stream leaves the column saturated, following the direct contact with the solution. This was due to the high rate of mass transfer between the bubbles and the liquid and the high surface area to volume ratio exerted by the bubbles. This can be reflected mathematically by substituting a high value for $k_v a$ and rearranging, simplifying the expression to:

$$\frac{dm}{dt} = \frac{Q_{air} . M_w . P^{SAT} \rho_v}{\rho_v RT - P^{SAT} M_w} \tag{2.0}$$

This model expression predicts a removal of liquid by evaporation which is a linear function of the gas flowrate, temperature, and solution vapour pressure, should these all remain constant.

The assumption that the vapour stream rapidly reaches saturation conditions is being continued in this work, and hence equation 2.0 is the starting point for the development of the evaporation model. This model is to be extended however, to allow for the inclusion of the effect of dissolved API upon the vapour pressure of the solution, and therefore reduced vapour pressures as modelled in section 3.3 are utilised instead of the constant values corresponding to pure solutions used by Roche et al (Roche, et al., 2020). This means that the

rate of evaporation is now a function of gas flowrate, temperature, and solute concentration in the solution as shown in equation 3.0:

$$\frac{dm}{dt} = \frac{Q_{air} . M_w . P^{SAT}(x_i, T)\rho_v}{\rho_v RT - P^{SAT}(x_i, T) M_w} \quad (3.0)$$

where x_i is the mass fraction of the solute in the solution.

4.2 Modelling the Overall System Mass Balance

For this work, the design of operation of the MSMPR is the primary influential factor for the process flow rates and their associated concentrations. The desired flow rate to the MSMPR is entirely dependent on the required slurry residence time in the vessel. The bubble column offers flexibility for solution throughput and concentration gradients of the continuous feed stream to the MSMPR.

According to equation 3.0, at a volumetric gas flow rate of 5L/min and fixed temperature of 60C, achievable evaporation rates as high as 30g/min are estimated for pure methanol. However, the rate is reduced to 19.5g/min under the same conditions for a 1M concentrated solution (figure 6).

This underlines the importance of accounting for the effect of solution concentration upon the evaporation rate as significant errors may arise in mass balances should it not be considered in the process design.

Using the evaporation rate profiles, developed using equation 3.0, it was possible to choose a desirable evaporation rate to achieve a concentration step, prior to the crystallization and to perform an overall system mass balance based on the requirements of the MSMPR.

The start-up system concentration profile was modelled to understand the approach to steady state by applying a component mass balance and applying a constant volume condition to simplify the expression:

The overall system mass balance can be described by:

$$F = \dot{m}_{evap} + O \tag{4.1}$$

A component mass balance can be described by:

$$F\,x_F = (O)\,x_W \pm \frac{d(W\,x_W)}{dt} \tag{4.2}$$

Substituting 4.1 into 4.2 :

$$F\,x_F - (F - \dot{m}_{evap})\,x_W = \pm \frac{d(W\,x_W)}{dt} \tag{4.3}$$

Applying the constant mass condition, achieved by the dip-tube at the outlet (assume change in solution density over time step is negligible), and conditions are such that the solution concentration is expected to increase:

$$F\,x_F - (F - \dot{m}_{evap})\,x_W = \frac{d(x_W)}{dt} W \tag{4.4}$$

Rearranging:

$$d\,t = W \frac{d(x_W)}{F\,x_F - (F - \dot{m}_{evap})\,x_W} \tag{4.5}$$

Integrating for $x_{W,}$ the solution concentration at a desired time point:

$$t_1 - t_0 = \frac{-W}{(F - \dot{m}_{evap})} \left| \log\left(F\,x_F - (F - \dot{m}_{evap})\,x_W\right) \right|_{x_{W_{t0}}}^{x_{W_{t1}}} \tag{4.6}$$

For t_0=0 and rearranging

$$\exp\left(-t_1 \frac{F - \dot{m}_{evap}}{W}\right) = \frac{F\,x_F - (F - \dot{m}_{evap})\,x_{Wt0}}{F\,x_F - (F - \dot{m}_{evap})\,x_{Wt1}} \tag{4.7}$$

Solving for x_{Wt1}

$$x_{W_{t1}} = \frac{F\,x_F - \dfrac{(F - \dot{m}_{evap})\,x_{Wt0}}{\exp\left(-t_1\left(\dfrac{F - \dot{m}_{evap}}{W}\right)\right)}}{F - \dot{m}_{evap}} \tag{4.8}$$

Where *F* - feed flow rate *(kg/s)*; *O* - outlet flow rate *(kg/s)*; *W* - mass within column *(kg)*; *x* - *mass fraction of paracetamol*; $\dot{m}_{evap}$ *– evaporation rate (kg/s)*; *t – time (s)*

This expression allows the effect of the volume of solution within the column on the start-up time to be illustrated and is described in further detail in section 5.2

5.0 Results and Discussion

5.1 Measurement of evaporation rate & model prediction comparison

Following the experimental method as outlined in section 3.1 the difference between the slopes of the linear fits to experimental data for each flow rate was taken as the rate of evaporation (figure 7). The change of mass in the column was attributed to be entirely due to the influence of the stripping effect of the gas stream.

An example result for such mass flow rate measurements during an experiment is seen in Figure 7. The slope of each line is taken as the averaged flow rate into the corresponding collection vessel over the duration of time measured. The ‘mass in’ profile shows the result of a successful pump calibration to a collection tank, yielding a flow rate of 8.6g/min. This was fed to the column and presumed to be constant for the entire experiment. The ‘mass out’ profile shows the experimentally achieved accumulation of the outlet stream from the column to a holding tank, 5.26g/min. The difference between the two slopes yields an achieved evaporation rate of 3.34g/min.

A summary of numerous such experiments conducted is presented in Table 2. Each experiment is performed using paracetamol in methanol solutions with the same feed concentration of 7% wt (~0.37M / 0.0741 g/g):

The evaporation rate of each experimental run was predicted using equation 3.0 and the saturation vapour values as described in section 3.3. For example, if an outlet concentration of 1M (17.6 wt%, 0.212 g/g) at a flow rate of 4.5g/min is desired, a mass balance is applied using equation 3.0 to determine the operating conditions required to achieve this. At a temperature of 50°C and a desired steady state concentration of 1M, the rate of

evaporation is defined by the gas flow rate according to equation 3.0, with results shown in Table 3.

From table 3, when the column was operated at 50°C with a gas flow rate of 3 L/min, a rate of Methanol evaporation of ~4.1 g/min was achieved for the desired concentration. To maintain this steady state concentration, a feed flow rate of 9 g/min at a concentration of 0.52M (9.6 wt%, 0.106 g/g) is required, ultimately achieving a 92.3% increase in the concentration of the solution.

5.2 Analysis of Start-Up and Approach to Steady-State Operation

The time duration for continuous processes to reach steady state can be impractically long due to the nature of the process. For example, a continuous crystallization process often takes up to six residence times to attain steady state operation due to the characteristic kinetics of the growth and nucleation rates of the crystals at the operating supersaturation level. This can take several hours depending on the design of the process. (Cole, et al., 2017; Wood, et al., 2019)

The time duration for start-up of the bubble column in a continuous processing configuration was assessed by keeping the temperature and gas flow rate constant, as well as the flowrate and concentration of the feed, as described in section 3.1. The concentration was measured periodically during this start-up period as illustrated in *Figure 8*. The sampling was more frequent at the initial stages to understand the approach to a steady state operation. Equation 4.8 was applied with the known parameters and the results of the predictive model yielded the profile shown in Figure 8.

The impact of total mass (operating volume) in the column from an initial starting point of concentration change was assessed by increasing the *W* parameter in equation 4.8 and the

results are shown in *Figure 9*. It can be seen that at constant gas flow rate and temperature, it takes a longer duration for the solution to reach the desired steady-state concentration value,

To minimise start up time, each experiment started with a 'dry loading', with the gas flow and temperature set prior to charging the column with the solution in-flow. The dip-tube maintained the volume constant once the solution was allowed to accumulate to the desired level. This enhanced the initial concentration increase rate, as having the column filled with dilute solution would significantly impact the duration to reach the desired steady state concentration, as shown in Figure 9. The effect of the dilute solution within the column can impact the time taken to reach steady state operation concentration from minutes to hours. It is desired to minimise this start up time to reach a steady state of concentration output. To achieve this, the process was repeated with the column 'dry loaded' for various gas flowrates, maintaining the outlet temperature steady at 40℃. The results are shown in Figure 10, with the model overlaying the experimental results.

For all conditions studied here, steady state operation is evident within 30 minutes of operation and can be maintained for a further two hours. This indicates that the column is capable of producing a consistent output for a significant operation duration. The relatively short start up time to reach steady state is particularly significant as it will not become a limiting factor in the design if this method is followed.

5.3 Effect of Gas Residence Time

The assumption of the gas reaching saturation is valid in this work as described by the results in the previous sections, and as observed by Roche et al (Roche, et al., 2020). However according to equation 1.0, the minimisation of gas residence time, due to reducing liquid

volume, will eventually cause a reduction of the rate of evaporation as it effectively approaches zero (due to the bubble column contents volume approaching zero). It was decided to vary the gas residence time in the column by lowering the height of the dip tube at the outlet, directly reducing the contact time between the two phases. The tube was lowered to desired, measured positions above the gas inlet and the rate of evaporation of solvent was measured by the same mass balance method as outlined in section 3.1. For practical purposes, the tube was not lowered lower than the feed inlet of the column: 7cm above the fritted base of the column (figure 11).

The rate of evaporation was measured for a continuous system designed to operate at a steady state concentration of 0.85M (15.2 wt%, 0.179 g/g), with a gas flow rate of 1 L/min and an operating temperature of 49℃. According to equation 3.0, this will produce a consistent rate of evaporation of ~1.20 g/min. A feed flow rate was provided at 2.1 g/min at a concentration of 0.36M (6.8 wt%, 0.072 g/g).

After allowing 20 minutes for the system to reach steady state, the dip tube position above the frit was lowered every ten minutes by a measured amount. Ten minutes was allotted between measurements to allow the system to regain steady state following the configuration disturbance. An averaged measurement of outlet flow rate and associated concentration was taken, as described in section 3.1. The measured rate of evaporation observed during the experiment is shown in Table 4 while Figure 12 shows the measured concentration of the outlet over time.

Following an initial 20-minute start up, the concentration profile reaches a consistent value for the remainder of the experiment, indicating an achievement of steady state operation regardless of the position of the dip tube and the residence time of the gas in the liquid. This

indicates that the saturation condition is still in effect even for the low residence times studied in this work (< 1 second, estimated by minimum bubble rise velocity (Mendelson, 1967)), and the simplified equation 3.0 is applicable here. As shown in table 4, the errors between the predicted rate of evaporation and that measured are appreciably low, underlining the accuracy of the model even in the case of reduced contact between the two phases.

5.4 Impact of Increasing Solution Throughput

To further assess the capabilities of the column, it was decided to analyse the impact of increasing the flow rate to the column under the same reduced volume conditions (i.e. lowered dip-tube). It is proposed that, if the gas flow rate and temperature are maintained, the only impact upon the rate of evaporation will be due to the change in concentration; brought about by a dilution effect imposed by the increased feed flow rate.

A continuous process was operated as described in section 3.1 while maintaining the gas flow rate and temperature of the vapour outlet constant at a flow rate of 2 L/min and 50°C respectively. The dip-tube within the column was maintained at 10cm height (figure 11) above the frit to ensure all feed solution could enter the column without fear of entrainment. Following equation 3.0 at steady state operation under these conditions, an evaporation rate of 2.62 g/min is predicted for an outlet concentration of 1M (17.6 wt%, 0.215 g/g) solution. The results are outlined in Figure 13 with the predictive model from equation 4.7 overlaying the experimental data. The measurements taken are shown in Table 5 with error percentages between the measured evaporation rate and the predicted rate.

The dilution effect of the outlet is seen by the associated decreasing dissolved concentration under the same fixed gas flow rate and temperature . The rate of evaporation was increased

to combat this effect and the experiment was repeated. This was achieved by increasing the flow rate of the gas inlet to 5 L/min, while maintaining the outlet temperature of the system at 50℃ by adjusting the control of the heat circulation system. Concentration measurements were taken after steady state operation was apparent by the outlet balance (30mins) and an average of the flow rate was measured.

Despite the reduced working volume by lowering the outlet dip tube, the evaporation rate remained consistent with model predictions once the temperature of the vapour stream out was controlled to the desired temperature. The throughput of the solution was increased to process a feed of 15g/min, achieving evaporation rates of up to 6.9 g/min of methanol in a single stage. The results are within acceptable percentage error margins of < 5% for all experiments performed based on comparison between experimental and predicted values. These results underline the potential applicability of the bubble column to achieve significant rates of evaporation for continuous manufacturing on an industrial scale in a single stage. The rate of evaporation is seen to be controllable within instrumentation accuracy and predictable by use of the modified model.

5.5 Downstream Processing & MSMPR Coupling

In this section, coupling of the bubble column to an MSMPR was configured as described in section 3.1 (figure 1), to assess the column's capability to perform as part of a continuous unit operation train. The MSMPR was designed to operate at a residence time of 40 minutes and a temperature of -5℃. The average working volume of the crystallizer was 80mL (76-84mL) and this was maintained by the dip-tube and periodic nitrogen pressurization of the headspace every 4 minutes, as described in section 3.2. For minimal disturbance to the steady state operation of the MSMPR, the volume accumulation was controlled to ensure

the volume did not increase by more than 10% during the pressurized transfers, as described by previous works (Hou, et al., 2014).

A continuous crystallization of paracetamol in methanol was decided on as a case study, due to its availability as an inexpensive API, and due to the availability of well-developed solubility profiles (Granberg & Rasmuson, 1999). For a residence time of 40 minutes, the inlet stream required delivery of a concentrated liquor solution at a target rate of 2mL/min. The column was configured between a feed tank of dilute paracetamol solution and the evaporation rate was predicted using equation 3.0 as previously shown.

A concentration of 0.255g/g (20.2 wt%; 1.158M) of paracetamol in methanol was to be achieved by continuous evaporation, offering a theoretical yield from the crystallizer of 31.6% at the decided operation conditions. The column was operated at a temperature of 40°C and a gas flow rate of 3L/min, resulting in an evaporation rate of 1.81/min of methanol using equation 3.0. To achieve an output of 2mL/min (1.58g/min), it was necessary to feed the column at a rate of 3.4g/min at a concentration of 0.092g/g (8.5 wt%; 0.454M). A 2L volume of feed solution was prepared and maintained at 40°C, as described in section 3.2 and delivered to the column by calibrated peristaltic pump.

Dissolved concentrations were taken for every residence time the column (triangles in Figure 14) and MSMPR (circles in Figure 14) were in operation. The output from the column can be seen to be steady at an average concentration of 0.257 g/g, with a measured variation of ±0.007 g/g. The mother liquor concentration can be seen to increase from the batch start-up and to reach an averaged measured value of 0.218g/g over five residence time measurements. The results of the crystallization experiment are summarised in Table 7.

Figure 15 shows the results of particle counts of a specified particle size range from the FBRM measuring in-situ (all particles <1000 micron). The trend is characteristic of an MSMPR process profile from a batch start-up; the initial sharp decrease in counts indicate the onset of a 'wash out' phase from the introduction of fresh supersaturated solution and the removal of accumulated volume aliquots by headspace pressurization and the submerged dip-tube. Steady state of operation of the MSMPR is evident from the plateaued value of the particle counts over the final two residence times. The brief dip shortly after the 7^{th} residence time was due to fouling and subsequent cleaning of the probe.

6.0 Conclusion

The performance of a bubble column has been investigated as a continuous evaporation unit operation for a pharmaceutical process stream. Evaporation rates up to 7g/min in a single equilibrium stage were achieved and a developed thermodynamic model predicted the rate to a significant degree of accuracy. The model accounted for the reduction of vapour pressure effect imposed by the dissolved solute and resulted in improved accuracies of the prediction of evaporation rate. The time taken to achieve a steady state of control of the column was also analysed and predicted to a significant degree using the model developed in this study. Industrial-scale throughput for continuous processing (up to 15g/min) was achieved in the column with minimised gas residence time by lowering the dip-tube at the outlet, indicating the column's capacity as a high throughput single stage equilibrium system.

Finally, as the column showed good stability and predictability, a continuous crystallization was successfully performed with the bubble column continuously concentrating the process feed stream. Steady state operation was evident by offline concentration measurements

and on-line FBRM particle tracking in-situ; indicating the applicability for the method in this configuration.

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