Supporting Information

Heat Transfer and Residence Time Distribution in Plug Flow Continuous Oscillatory Baffled Crystallisers

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KEYWORDS

Residence time distribution, heat transfer, continuous oscillatory baffled flow, plug flow, oscillatory flow, axial dispersion, continuous crystallisation
1. Continuous Oscillatory Baffled Crystalliser Theory and Operation

The basic principle of the continuous oscillatory baffled crystalliser (COBC) stems from a series of periodically spaced orifice baffles on to which an oscillation is applied. As the flow interacts with the baffles, eddies are created. This repeating oscillation cycle ensures strong radial mixing. Figure S1 illustrates the flow interactions inside the COBC.

![Figure S1. Flow interaction within baffled tubes. Photograph of baffles with flow patterns superimposed. Eddies are generated due to oscillatory flow.](image)

The ability to extend the mean residence time, under plug flow conditions, at a similar mixing intensity, is advantageous to slow processes such as crystallisation, where there is a need for longer residence times. For example, a 25 m DN15 COBC operating under oscillatory conditions of 1 Hz, with a 30 mm amplitude and a flow rate of 50 g min\(^{-1}\) has a residence time of approximately 90 minutes, where Re\(_o\) = 1500 and Re\(_n\) = 65. To achieve comparable mixing intensity in a non-baffled and non-oscillated tubular system of the same dimensions, the net flow rate would need to be increased from 50 g min\(^{-1}\) to 1200 g min\(^{-1}\), which would result in an approximate residence time of only 4 minutes i.e., 5% of oscillatory baffle flow.

When utilizing oscillatory flow technology there are namely three variables that may be selected for operation for a fixed reactor length, oscillatory frequency, oscillatory amplitude and net flow rate.\(^1\),\(^2\) Selection of optimal conditions will be dictated by the process, for example oscillatory conditions will be selected which are capable of suspending material at completed desupersaturation, also for a fixed length of a system a particular residence time is required, to achieve sufficient growth and size of the resulting particle. To achieve this various oscillatory conditions, residence times and net flow rates will be employed depending on the compound of interest investigated and associated crystallisation kinetics. Thus, a range of operating conditions within the system needs to be studied to provide an operation design space for crystallisation applications.
2. Residence Time Distribution Measurements in Literature

There have been many studies measuring residence time distributions (RTDs) in oscillatory flow systems with a wide range of geometries and operating conditions. From these studies it has been found that ideal operating conditions include working within velocity ratios between 2 – 10 and $Re_o \geq 100$. Table S1 shows a summary of these previous reports on RTD behaviour within oscillatory flow systems. The range of geometries makes it difficult to make appropriate comparisons.

Table S1. Previous RTD studies of oscillatory baffled mixing technologies.$^{3-14}$

| Tube ID (mm) | System length (m) | $BS_r$ ID (mm) | Baffle ID (mm) | $\alpha$ | $Re_n$ | $Re_o$ | $St$ | Results |
|-------------|------------------|----------------|----------------|---------|--------|--------|------|---------|
| 23          | 0.67             | 1.5            | 13             | 0.44    | 110    | 100 - 3300 | 0.3 - 9 | $D/uL$: 0.025 - 0.128 |
| 51          | 2.5              | 1.5            | 32             | 0.61    | 40, 106 | 160 - 2500 | 0.8, 2 | $1/Pe$: 0.8 - 2 |
| 25          | 1.08             | 1.5            | 16             | 0.34    | 128    | 40 - 3600 | 0.35 - 4 | $D/uL$: 0.030 - 0.10 |
| 25          | 6.3              | 1.5            | 16             | 0.34    | 106 - 3400 | 100 - 750 | 0.4 - 3 | $D/uL$: 0.003 - 0.012 |
| 23.5        | 2.9              | 1.5            | 12             | 95, 127, 190, 252 | 0 - 2500 | 0.4 - 3.8 | tanks-in-series model |
| 40          | 25               | 1.8            | 32             | 0.21    | 160-250 | 2000 - 8000 | 0.4 - 0.8 | $D/uL$: 0.8 - 1.6 |
| 50          | 0.5              | 1.5            | 11             | 0.78    | 500 - 6000 | 500 - 1600 | 1.0 | Axial dispersion (batch) |
| 4.4         | 3.0              | 1.6            | 0.87           | 0 - 1600 | $D/uL$ minimum when $Re_o = 100 - 300$ |
| 5           | 9                | 3              | 1.6            | 0.87    | 10 - 58 | 100 - 1000 | 0.08 - 0.4 | Axial dispersion |

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3. Full Description of Experimental Conditions and Data Fitting for Residence Time Distribution Studies

The full set of operating conditions for the RTD measurements performed in this work are listed in Table S2.

**Table S2.** Experimental conditions for residence time distribution studies.

| Amplitude (mm) | Frequency (Hz) | Flow Rate (g/min) |
|----------------|----------------|------------------|
| 38             | 1              | 50               |
| 38             | 1              | 50               |
| 38             | 1              | 200              |
| 38             | 1              | 200              |
| 66             | 1              | 50               |
| 66             | 1              | 50               |
| 66             | 1              | 200              |
| 66             | 1              | 200              |
| 9              | 3              | 50               |
| 9              | 3              | 50               |
| 30             | 3              | 200              |
| 30             | 3              | 200              |
| 14             | 3              | 50               |
| 14             | 3              | 50               |

The experimental data were fitted to a plug flow with axial dispersion model exploiting the imperfect pulse technique. A detailed explanation of this procedure is given here. The axial dispersion, $E$, was obtained by solving the following equation:\(^{15}\)

$$\sigma^2 = \frac{\sigma_t^2}{\tau^2} \left[ 2 \left( \frac{E}{\nu} \right) - 2 \left( \frac{E}{\nu} \right)^2 \left( 1 - e^{-\frac{\nu}{T}} \right) \right]$$

where $\sigma^2$ is variance i.e., a measure of the spread of the RTD curve. The mean residence time, $\tau$, was calculated from the experimental concentration and time data using:

$$\tau = \frac{\Sigma t_i C_i \Delta t_i}{\Sigma C_i \Delta t_i} = \frac{\Sigma t_i C_i}{\Sigma C_i}$$
where $t_i$ is the experimental time with a given concentration, $C_i$. The variance, is calculated using:

$$\sigma^2 = \frac{\sum t_i^2 C_i \Delta t_i}{\sum C_i \Delta t_i} - \left[ \frac{\sum t_i C_i \Delta t_i}{\sum C_i \Delta t_i} \right]^2 = \frac{\sum t_i^2 C_i}{\sum C_i} - \frac{\left[ \sum t_i C_i \right]^2}{\sum C_i}$$

Given experimentally a perfect pulse of tracer cannot be achieved, the imperfect pulse method is applied to provide a more realistic description of the experimental tracer profile.

The imperfect pulse method for determining axial dispersion accounts for the finite dispersion of tracer concentration over the duration of the injection. The basic differential equation representing the dispersion model, used previously to describe dispersion in oscillatory flow mixing, is represented by:

$$\frac{\partial C}{\partial \theta} = \left( \frac{E}{uL} \right) \frac{\partial^2 C}{\partial Z^2} - \frac{\partial C}{\partial Z}$$

where $C$ is the normalised concentration; $\theta$ is dimensionless time, $\theta = ut/L$; $Z$ is dimensionless length, $Z = x/L$; $u$ (m s$^{-1}$) is the mean axial velocity; $L$ (m) is the length of reactor used; $E$ (m$^2$ s$^{-1}$) is the axial dispersion coefficient; and $t$ is time, measured from the tracer injection. This differential equation permits the prediction of pulse profile, from the calculated axial dispersion coefficient, downstream from the original measurement. This equation permits the prediction of a pulse profile, from the calculated axial dispersion coefficient, downstream from the original measurement.

The imperfect pulse model was fitted to experimental data, and completed using procedures described in detail elsewhere. Concentrations were normalised using the following equation:

$$C(t) = \frac{c(t)}{\int_0^\infty c(t) dt} = \frac{C_{pulse}}{M \nu} = \frac{C_i}{\sum C_i \Delta t_i}$$

The mass of tracer flowing through the system was calculated from the area under the RTD curve (summation of $C_i \Delta t_i$), where $M$ is the mass of tracer (kg) and $\nu$ is fluid velocity m$^3$ s$^{-1}$. This material balance allows confirmation of tracer recovery once the experiment is complete.
A transfer function, $TR(t)$, was applied to convert the upstream response to the downstream response, described by:

$$TR(t) = \frac{\text{Pe} \tau}{\sqrt{4 \pi t}} \exp \left( -\frac{\text{Pe} t^2}{4t} \left( 1 - \frac{t}{\tau} \right)^2 \right)$$

Using the $Pe$ number, the axial dispersion coefficient was calculated. The model response $C_2(t)'$ at position 2 was calculated by convolving the measured input response $C_1(t)'$ and the model transfer function $TR(t)$:

$$C_2(t)' = \int_0^t TR(t - p) C_1(p) dp.$$  

where $p$ is the time response downstream and $t$ is the time response from the upstream response. The model calculated response $C_2(t)'$ was then compared to the experimental $C_2(t)$ using the target function defined as:

$$\Delta C = \sum_{i=1}^{N} \left( C_2(t_i) - C_2(t_i)' \right)^2$$

The $Pe$ number was varied to find the value resulting in minimal difference between the calculated and predicted responses, this value was taken as the $Pe$ number of the system. A representative result obtained using this fitting procedure is shown in Figure S2. Using the Pe number obtained from the minimal difference between predicted and observed values, an overlay of the raw data with the predicted response can be plotted (Figure S2, right panel).

**Figure S2.** Application of Peclet number. Difference plot (left) used to determine the Peclet number, and representative concentration data (right, dotted and solid black; 100 g/min, 30 mm amplitude, 1 Hz), with the model response overlaid (orange).
4. Full Experimental Conditions and Temperature Data for Heat Transfer Studies

The full set of experimental conditions for the heat transfer studies are given in Table S3.

Table S3. Experimental conditions for heat transfer studies.

| Oscillation Setup | Solution Mass Flow Rate (g/min) | Jacket Mass Flow Rate (g/min) |
|-------------------|---------------------------------|-------------------------------|
| Single            | 50                              | 50                            |
| Single            | 50                              | 250                           |
| Single            | 50                              | 500                           |
| Single            | 50                              | 750                           |
| Single            | 50                              | 1000                          |
| Single            | 50                              | 1700                          |
| Single            | 50                              | 2700                          |
| Single            | 100                             | 100                           |
| Single            | 150                             | 150                           |
| Single            | 200                             | 200                           |
| Single            | 200                             | 1700                          |
| Single            | 200                             | 2700                          |
| Double            | 50                              | 25                            |
| Double            | 50                              | 50                            |
| Double            | 100                             | 100                           |
| Double            | 150                             | 75                            |
| Double            | 150                             | 81                            |
| Double            | 150                             | 89                            |
| Double            | 150                             | 150                           |
| Double            | 150                             | 162                           |
| Double            | 200                             | 200                           |
| Double            | 200                             | 220                           |
| Double            | 200                             | 240                           |
The full experimental temperature data obtained from single and double oscillations setups can be found in Figure S3 and Figure S4 respectively.

**Figure S3.** Experimental temperature data for all single oscillation experiments. The data have been connected by lines as a guide (lines do not represent the actual profile).
Figure S4. Experimental temperature data for all double oscillation experiments. The data have been connected by lines as a guide (lines do not represent the actual profile).

5. Full Description of Temperature Profile Model

A method for determining the overall heat transfer coefficient ($U$) for oscillatory flow in baffled tubes from experimental temperature data has been outlined previously.\textsuperscript{16} Firstly, it considers that $U$ can be determined from the following equation for the heat transfer rate ($Q$):

$$Q = A U \Delta T_{lm} = Q_{sol} = m_1 c_p \Delta T_{sol}$$

Secondly, it considers that the log mean temperature difference ($\Delta T_{lm}$) over a COBC section can be given by:

$$\Delta T_{lm} = \frac{\Delta T_2 - \Delta T_1}{ln \left( \frac{\Delta T_2}{\Delta T_1} \right)}$$

$$\Delta T_1 = T_{ln} - T_2$$

$$\Delta T_2 = T_{out} - T_1$$
By substituting the expression for the log mean temperature difference into the expression for \( Q \), the overall heat transfer coefficient for a COBC section can be determined by the following equation:

\[
U = \frac{m_1 c_p \Delta T_{sol}}{A \Delta T_{lm}}
\]

\[A = \pi d_t L\]

The values in these expressions are the mass flow rate of the solution (\( m_1 \)); the specific heat capacity of the solution (\( c_p \)); the total heat transfer area of the COBC section based on its inner diameter (\( A \)); the inlet and outlet temperatures of the solution (\( T_{in} \) and \( T_{out} \)); the inlet and outlet temperatures of the jacket fluid (\( T_1 \) and \( T_2 \)), the temperature difference in the solution (\( \Delta T_{sol} \)) and the temperature difference in the jacket fluid (\( \Delta T_j \)).

According to Newton’s law of cooling/heating, the temperature of the solution (\( T_1 \)) will vary along the COBC length (\( x \)) according to the following differential equation:

\[
\frac{dT_1}{dx} = k_1(T_2 - T_1)
\]

When the solution flows through a straight \( T_2 \) represents the temperature of the jacket fluid and when the solution flows through an unjacketed bend \( T_2 \) represents the temperature of the surrounding air. Assuming plug flow in the COBC, the constant (\( k_1 \)) in the differential equation is given by:

\[
k_1 = \frac{U_1 a_1 A_{xs1}}{m_1 c_p}
\]

\[a_1 = \frac{4}{d_t}\]

\[A_{xs1} = \pi d_t^2/4\]

The values in these expressions are the heat exchange area per unit volume (\( a_1 \)), the cross-sectional area based on the inner diameter (\( A_{xs1} \)), the mass flow rate of the solution (\( m_1 \)) and the specific heat capacities of the solution (\( c_p \)).

Using the overall heat transfer coefficients, and making certain assumptions, the temperature profile along the COBC can be modelled. Depending on which assumptions are made, the temperature profile model can have three levels. Level 1 assumes that the jacket fluid
temperature is constant and that there are no heat losses from the jacket. Level 2 assumes that
the jacket fluid varies and that there are no heat losses from the jacket. Level 3 assumes that
the jacket fluid varies and that there are heat losses from the jacket. For each level, the
relevant differential equations must be solved either numerically or analytically in order to
model the temperature profile along the COBC.

**Level 1: Constant Jacket Fluid Temperature, No Losses**

Differential Equations

\[
\frac{dT_1}{dx} = k_1(T_2 - T_1)
\]

\[
\frac{dT_2}{dx} = 0
\]

\[
k_1 = \frac{U_1 a_1 A_{xs1}}{m_1 c_{p1}}
\]

General Analytical Solution

\[
T_1(x) = T_2 + (T_{10} - T_2) e^{-k_1 x}
\]

\[
T_2(x) = T_2
\]

**Level 2: Variable Jacket Fluid Temperature, No Losses**

Differential Equations

\[
\frac{dT_1}{dx} = k_1(T_2 - T_1)
\]

\[
\frac{dT_2}{dx} = -k_2(T_1 - T_2)
\]

\[
k_1 = \frac{U_1 a_1 A_{xs1}}{m_1 c_{p1}}
\]

\[
k_2 = \frac{U_1 a_1 A_{xs1}}{m_2 c_{p2}}
\]

General Analytical Solution

\[
T_1(x) = C_1 + C_2 e^{(-k_1 + k_2)x}
\]

\[
T_2(x) = \frac{C_2 e^{(-k_1 + k_2)x} k_2}{k_1} + C_1
\]
\[ C_1 = \frac{T_{20} - T_{10}\left(\frac{k_2}{k_1}\right)}{1 - \left(\frac{k_2}{k_1}\right)} \]

\[ C_2 = T_{10} - C_1 \]

**Level 3: Variable Jacket Fluid Temperature, Losses**

**Differential Equations**

\[ \frac{dT_1}{dx} = k_1(T_2 - T_1) \]

\[ \frac{dT_2}{dx} = -k_2T_1 + (k_2 + k_3)T_2 - k_3T_a \]

\[ k_1 = \frac{U_1 a_1 A_{xx1}}{m_1 c_p1} \]

\[ k_2 = \frac{U_1 a_1 A_{xx1}}{m_2 c_p2} \]

\[ k_3 = \frac{U_2 a_2 A_{xx2}}{m_2 c_p2} \]

\[ a_2 = \frac{4}{(d_s - d_t)} \]

\[ A_{xx2} = \left(\pi \frac{d_s^2}{4}\right) - \left(\pi \frac{d_t^2}{4}\right) \]

**General Analytical Solution**

\[ T_1(x) = e^{(S + R)x} C_2 + e^{(S - R)x} C_1 + T_a \]

\[ T_2(x) = \frac{1}{k_1}[(S + R) e^{(S + R)x} C_2 + (S - R) e^{(S - R)x} C_1 + k_1(e^{(S + R)x} C_2 + e^{(S - R)x} C_1 + T_a)] \]

\[ C_1 = \frac{T_{20}k_1 - T_{10}[S + R + k_1] - T_a[-S - R]}{-2R} \]

\[ C_2 = T_{10} - T_a - C_1 \]

\[ S = \frac{1}{2}(-k_1 + k_2 + k_3) \]

\[ R = \frac{1}{2}\sqrt{k_1^2 - 2k_1 k_2 + 2k_1 k_3 + k_2^2 + 2k_2 k_3 + k_3^2} \]
The extra terms which arise in levels 2 & 3 of the temperature profile model are, $m_2$ = mass flow rate of jacket fluid (kg s$^{-1}$), $c_{p2}$ = specific heat capacity of jacket fluid (J/kg °C), $d_s$ = inner diameter of the shell (m), $a_2$ = the heat exchange area per unit volume with respect to the shell (m$^{-1}$), $A_{xs2}$ = cross-sectional area with respect to the shell (m$^2$), $T_{10}$ = initial temperature of solution (°C), $T_{20}$ = initial temperature of jacket fluid (°C), $T_a$ = air temperature (°C), $k_1$, $k_2$ & $k_3$ = differential equation constants (-), $C_1$ & $C_2$ = integration constants (-), and $R$ & $S$ = substitution constants (-).

6. Temperature and Supersaturation Profile Modelling for Crystallisation Process Design in the Continuous Oscillatory Baffled Crystalliser

This case study looks at the seeded cooling crystallisation of paracetamol in a Water/IPA (60/40 wt%) solvent mixture as a continuous process in the DN15 COBC. The assumptions for this case study are as follows:

- It is a seeded crystallisation process (no nucleation, only growth)
- The seed crystals are cubic, the same size and grow equally in all directions
- Growth rate constant and growth order are independent of crystal size and temperature
- The process is operating under plug flow conditions
- A counter-current cooling system is being utilised
- The jacket temperature remains constant

In order to implement the model, the solubility of paracetamol in this solvent system must be known over the temperature range which is explored. Solubility data for this system have been obtained previously$^{17}$ and are plotted in Figure S5.
The equation used to fit this solubility curve is as follows:

\[ C_S = 0.0706 \, e^{0.0315 \cdot T_1} \]

The experimental procedure involves cooling a saturated paracetamol solution from 70 °C to a certain extent over a fixed COBC length (5.5m). Utilising a particular overall heat transfer coefficient (cooling method) will result in the solution being cooled to a particular final temperature over the COBC length. Using a basis of 1 kg solvent, the values of the constants involved in modelling the temperature and supersaturation profiles throughout the crystallisation process are listed in Table S4.

**Table S4.** Full list of constants involved in modelling the temperature and supersaturation profiles.

| Constant                | Symbol (Unit) | Value       |
|-------------------------|---------------|-------------|
| Growth rate constant    | \(k_g\) (m/s) | 1 x 10^{-6} |
| Growth order            | \(n\) (-)    | 1.5         |
| Solvent mass            | \(m_s\) (kg) | 1           |
| Total mass of API       | \(m_t\) (kg) | 0.6404      |
| Initial seed loading    | \(m_{x0}\) (wt%) | 1         |
| Crystal density         | \(\rho_c\) (kg/m^3) | 1260       |
Initial diameter of seeds $d$ (µm) 20
Solution mass flow rate $m_1$ (g/min) 50
Specific heat capacity $c_p$ (J/kg °C) 4180
Area per unit volume $a_1$ (m$^{-1}$) 266.7
Cross-sectional area $A_{xs1}$ (m$^2$) 0.000177
Initial solution temperature $T_{10}$ (°C) 70
Jacket temperature $T_2$ (°C) 20
Solution velocity $v$ (m/s) 0.004716
Overall heat transfer coefficient (1) $U_1$ (W/m$^2$ K) 25
Overall heat transfer coefficient (2) $U_2$ (W/m$^2$ K) 100
Overall heat transfer coefficient (3) $U_3$ (W/m$^2$ K) 400

The variables which will change over the course of the crystallisation process as they are being determined by the model are given in Table S5.

**Table S5.** List of variables determined by the model.

| Variable                          | Symbol (Unit)                  |
|-----------------------------------|--------------------------------|
| Mass of API in solid phase        | $m_x$ (kg)                     |
| Solution temperature              | $T_1$ (°C)                     |
| Solution concentration            | $C$ (kg/kg solvent)            |
| Saturation concentration          | $C_s$ (kg/kg solvent)          |
| Relative supersaturation          | $S$ (-)                        |
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