

# Reaction Engineering Evaluation and Utilization of Static Mixer Technology for the Synthesis of Pharmaceuticals

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## Abstract:

As part of an evaluation of equipment aimed at process intensification, the use of a continuously operating tubular reactor packed with static mixing elements (intensified plug flow reactor, IPFR) was investigated. A characterisation of the reactor was initially carried out and revealed close to ideal plug flow and good heat-transfer characteristics. An exothermic chemical reaction to synthesise a drug intermediate, where selectivity was known to be dependent on mixing efficiency and temperature profile, was carried out in the reactor. The results showed that the turbulent flow behaviour and the efficient temperature control led to high conversion of the starting material at high product yield and very low impurity levels. The IPFR was also found to be a useful tool for the determination of reaction kinetics.

## Introduction

Over the past few years, the pharmaceuticals and fine chemicals industry have shown an increasing interest in considering process intensified technology as a viable alternative to manufacture in traditional stirred tank reactors.<sup>1–6</sup> Drivers for this are considerably reduced capital investment cost, reliable scale-up, and increased inherent safety due to a relatively small reacting inventory. Although continuous processing technologies such as static mixers have been successfully used in the oil industry for a significant length of time,<sup>7</sup> literature about their application to the manufacture of active pharmaceutical ingredients (APIs), drug intermediates, or fine chemicals is limited.<sup>8–10</sup>

However, these mixer units could prove to be of particular advantage as they offer the potential for achieving liquid-phase plug flow at relatively low Reynolds numbers and high residence times, without the traditionally required major increase in reactor volume or flow velocity.<sup>11</sup> Similar performance can also be achieved through oscillatory flow<sup>12</sup> but this will not be discussed here.

A laboratory-scale rig was therefore built in-house at GlaxoSmithKline, R&D Tonbridge, to evaluate the suitability of such an “intensified plug flow reactor” (IPFR) technology for the synthesis of pharmaceuticals.

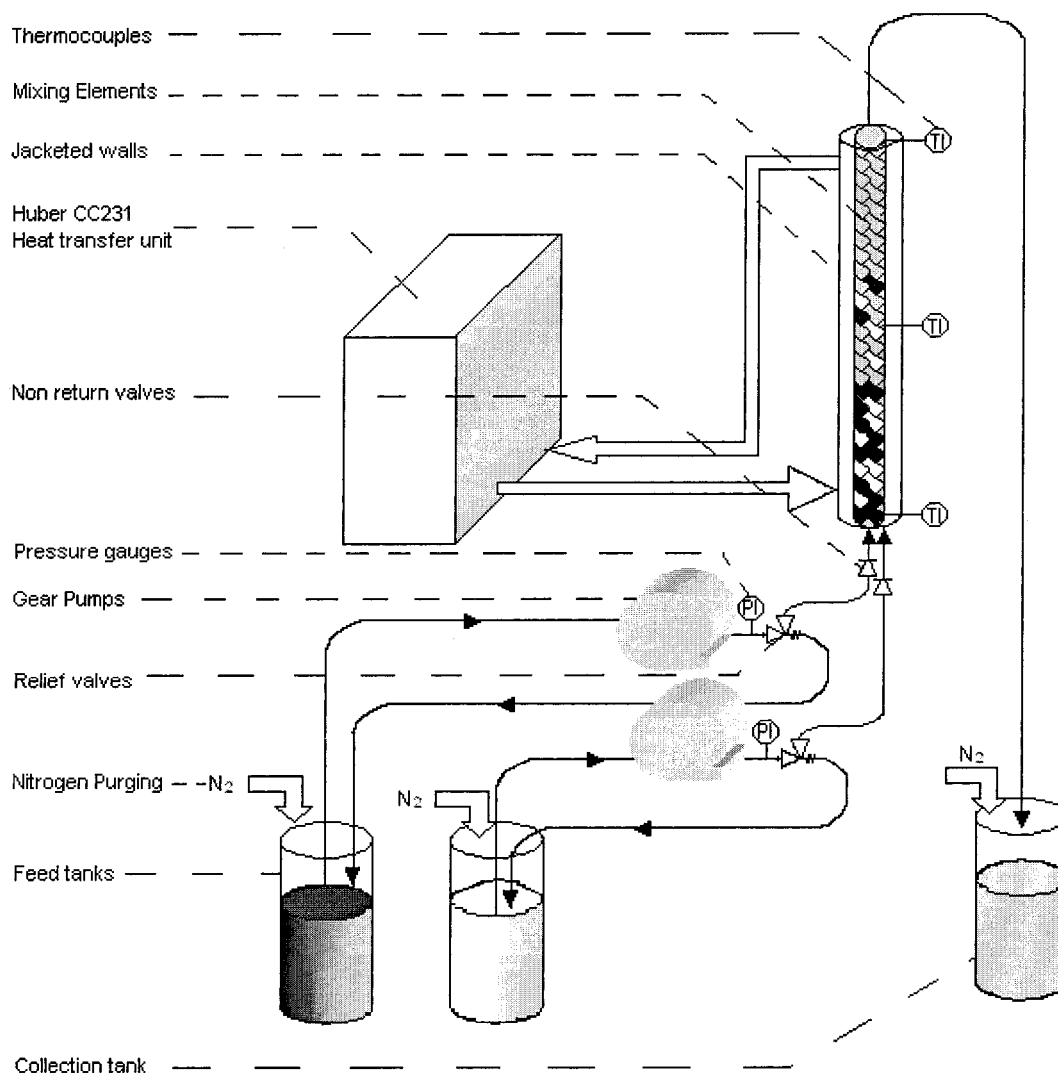
**Description of Equipment.** Figure 1 shows a schematic diagram of the IPFR. Two preheated/–cooled streams containing reactive reagents can be fed from two jacketed feed tanks via two separately controlled gear pumps into the tubular reactor. These Micropumps were controlled by inverters, allowing a combined total flow range from 30 to 400 mL·min<sup>–1</sup>. Both pump outlets were fitted with pressure gauges and nonreturn valves to ensure that over-pressurisation and back flow would not occur in the feed lines. As for the tubular reactor, two versions were built: one in glass for initial observation and demonstration purposes and one in SS316 to carry out reactions.

Both reactors were fitted vertically and had an internal diameter of 25.4 mm and a length of 750 mm, creating a total liquid hold-up volume of 350 mL. They could be fitted with precision-diameter Halar ETFE Sulzer SMV mixing elements. Halar ETFE was chosen as the material of construction for the mixing elements as it offers good resistance to most chemicals commonly encountered in pharmaceutical processes. The SMV geometry was selected on considerations regarding versatility. These elements can handle low-viscosity solvents but also gas/liquid systems and immiscible liquids of medium viscosity without generating excessive pressure drop,<sup>7</sup> which would have affected the pumps. The reactor could be heated or cooled by a heat-transfer fluid (silicone oil) flowing in the jacket over the whole length of the reactor. Using the silicone oil with a

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**Figure 1.** Schematic diagram of the IPFR rig.

Huber CC231 heat transfer unit allowed a wide temperature range for the experiments from  $-30$  to  $250$  °C.

The receiver tank was also jacketed to allow quenching of the reacted stream, if necessary. All equipment was suitably earthed and fitted within a metal framework in a walk-in fume cupboard. Sampling points were installed at the pumps outlets and at the reactor inlets and outlet. Three K-type thermocouples were fitted in the reactor: at the mixing point of the two inlet streams, at mid-length of the reactor, and at the outlet of the reactor.

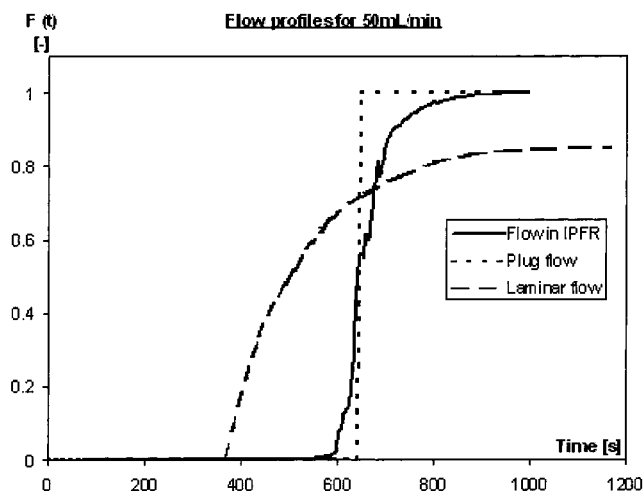
To prevent over-pressurisation of the set-up in the event of line or reactor blockage, a pressure relief valve was fitted on the reactor, and two additional pressure relief valves were fitted immediately after the pumps and linked to a recirculation loop to the feed tanks.

**Characterisation of the Equipment.** Prior to the investigation of any organic processes, it was deemed necessary to carry out a thorough characterisation to assess the performance capabilities of the reactor with regards to flow behaviour and heat transfer. This was done to allow matching the capabilities of the equipment with the requirements of the chemistry at a later stage.

**Tracer Experiments.** A hydrodynamic characterisation of the tubular reactor was carried out to check the impact of using static mixing elements on the flow behaviour, while also gaining a better understanding of the equipment's capabilities. The objective was to acquire data such as the time to reach steady state and the extent of axial diffusion, as these quantities have an impact on material consumption and expected purity profile for chemistry experiments.

A first set of experiments was done in the glass reactor with dye in a homogeneous system to identify any shortcomings of the initially chosen design. A nonjacketed dead zone at the feed inlets of the reactor was immediately identified. Modifications to the SS316 reactor inlet were carried out, so that the liquid entering the reactor could be instantly cooled or heated. Another discovery that resulted from these visual tracer experiments was that the flow was still benefiting from the "static mixing" effect one-element length after a static mixer element.

Therefore, it was recognised that instead of 30 mixing elements to completely pack the reactor, only 13 accordingly spaced elements were needed to achieve the same effect, which has positive effects on capital expenditure through



**Figure 2.**  $F$  curves for plug flow, laminar flow, and the IPFR reactor at 50 mL/min.

reduced number of reactor inserts and a resulting lower pressure drop. The SMV elements were also oriented at 90° relative to each other as recommended by the supplier<sup>7</sup> to further promote the creation of turbulence by radial mixing.

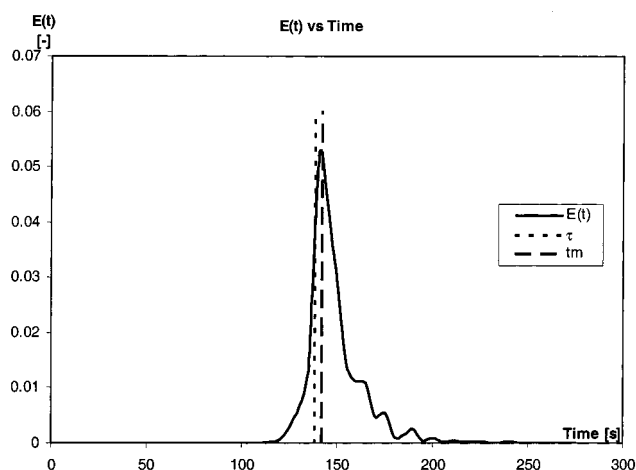
After these qualitative investigations in the glass reactors, a quantitative study in the accordingly modified stainless steel reactor was carried out to quantify the flow behaviour and obtain information on the residence time distribution. The experimental procedure was as follows:

Deionised water was pumped through the installation at a fixed flow-rate. The feed was then switched from the deionised water tank to a tank containing a 1 M potassium chloride electrolyte solution. The changes in the conductivity at reactor outlet were recorded via a Knick Portamess 910 portable conductivity meter. The conductivity data were then transferred to Microsoft Excel for postprocessing and also normalised to the steady-state value. The so-obtained dimensionless form of the conductivity curve over time is called the  $F$  curve.

This method, defined as the step method via a Heavyside pulse, is considered more reliable and easier to implement practically than the pulse method through a Dirac impulse,<sup>12</sup> which consists of the injection of a known amount of tracer in the feed. Four flow rates were investigated: 50, 100, 150, and 200 mL/min, which equates to empty-tube Reynolds numbers of 42, 84, 125, and 167, respectively. Figure 2 shows an example of tracer plots obtained on the IPFR in comparison to laminar and ideal plug flow.

As can be observed, with static mixing elements present the profile of the tracer is closer to the ideal curve of a plug flow reactor than to the laminar flow curve. This is a somewhat surprising result, since this behaviour is not expected for such low Reynolds numbers. Similar curves were also obtained at the higher flow rates investigated.

These plots were also used to obtain information on the residence time distribution (RTD). The residence time distribution function  $E(t)$  describes how much time different fluid elements have spent in the installation. It is derived by



**Figure 3.** Residence time distribution  $E(t)$  for 200 mL/min.

numeric differentiation (eq A<sup>13</sup>) from the  $F$  curve shown in Figure 2.

$$E(t) = \frac{dF(t)}{dt} \quad (\text{A})$$

Figure 3 shows the residence time distribution function over time for a flow-rate of 200 mL/min. It also contains the mean residence time, which was calculated using equation B.<sup>14</sup>

$$t_m = \int_0^{\infty} t \cdot E(t) dt \quad (\text{B})$$

The position of the measured mean residence time ( $t_m$ ) relative to the space time ( $\tau$ ), which is the time all fluid elements should spend ideally in the reactor, helps to spot flow problems. If the space time is significantly smaller than the mean residence time, then there are some dead zones in the reactor. If the space time is considerably larger than  $t_m$ , channeling is occurring.<sup>13</sup> This effect can specifically occur in packed-bed reactors such as the IPFR and would mean that the reacting stream is split into sections that do not stay the same amount time in the reactor, which could lead to variations in conversion or to the creation of impurities.

As can be observed on the graph, the space time almost matches the mean residence time. This illustrates the near ideal plug-flow characteristics of the rig and could be consistently observed at all four flows investigated.

From the tracer experiments, the ideality of the IPFR installation was further quantified by reactor modelling using the Bodenstein number. This dimensionless number describes the degree of back-mixing in a tubular reactor and is defined as the ratio of transport by convection to that by axial diffusion. At high Bodenstein numbers ( $Bo > 100$ ), a reactor is considered close to an ideal plug flow reactor ( $Bo \rightarrow \infty$ ), and at low Bodenstein numbers, close to a completely back-mixed tank ( $Bo \rightarrow 0$  is equivalent to a continuously stirred tank reactor).<sup>15</sup>

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**Table 1.** Bodenstein number and tanks in cascade for tracer experiments

flow [mL/min]	Bodenstein number	number of tanks in cascade
100	134	67
200	369	185

The Bodenstein number can be calculated from the residence time distribution using Danckwert's approximation according to equation C.<sup>16</sup>

$$\tan \alpha = \frac{1}{2} \sqrt{\frac{Bo}{\pi}} \approx \sqrt{\frac{N}{2\pi}} \quad (C)$$

The value of  $\alpha$  is defined as the angle of the tangent on the  $F$  curve at  $t = \tau$ . Equation D is only valid for  $Bo \gg 10$ . As can be observed from Table 1, the Bodenstein numbers obtained from the experimental plots are high and above 100. This confirms that the mixing elements improve the flow profile towards an ideal plug flow.

The Bodenstein number can be further used to estimate the number of ideal, back-mixed tanks in series ( $N$ ) required to reproduce the behaviour of the installation (eq D<sup>16</sup>).

$$N = \frac{Bo}{2} \quad (D)$$

Again, Table 1 shows some selected results obtained from the tracer experiments. When the flow and therefore the induced turbulence is increased, the number of tanks in series and the Bodenstein number also increase as expected.

As discussed, the values for the Bodenstein number and the number of back-mixed tanks in series for the IPFR were high, which again strongly suggests close to ideal plug-flow behaviour,<sup>17</sup> even at comparatively low empty-tube Reynolds numbers. Therefore, it was concluded that with respect to reactor modelling, the IPFR could be safely considered as having ideal plug flow in a first approximation.

**Heat Transfer.** Knowing the heat-transfer efficiency and particularly the overall heat-transfer coefficient,  $U$ , is essential for effective temperature control and safe operation of a reactor. To determine  $U$ , six experiments were carried out varying two main parameters: process flow-rate and heat-transfer unit temperature (heat-transfer fluid flow was predefined by the Huber system). The flow rate of water pumped through the reactor was set at 50, 150, and 300 mL/min (which corresponds to empty tube Reynolds numbers of 42, 125, and 251, respectively) and the heat transfer unit temperature set at 10 and 60 °C for each flow rate. The outlet temperature of the water was then measured until steady state was reached. From the experimental data, the overall heat-transfer coefficients were estimated by a simple heat balance (eq E<sup>18</sup>).

$$\dot{m} \cdot C_{\text{pf}} \cdot (T_{\text{fi}} - T_{\text{fo}}) = U \cdot A \cdot (\Delta T_{\text{fm ln}} - T_{\text{j}}) \quad (E)$$

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**Table 2.** Heat-transfer data

flow rate [mL/min]	jacket temperature [°C]	heat-transfer coefficient $U$ [ $\text{W} \cdot \text{m}^{-2} \cdot \text{K}^{-1}$ ]
300	60	268.4
	10	292.3
150	60	179.9
	10	210.0
50	60	93.3
	10	131.6

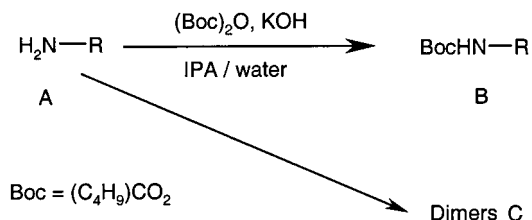
**Scheme 1.** Boc protection of an amine

Table 2 shows the data obtained for the operating parameters investigated.

The relatively high  $U$  values obtained experimentally were due to the beneficial impact of the mixing elements on the flow. By breaking up the flow and promoting radial mixing, the SMV static elements reduce the layering effect of laminar flow, especially near the reactor wall, thus improving overall heat transfer.<sup>7</sup> From this we could deduce that the reactor would be suitable for investigating exothermic reactions.

**Process.** The characterisation of the reactor gave us confidence that it would be compatible with the process we intended to study and also that we had reason to expect process improvements over a classic semibatch mode. This chemical reaction involved the protection of an amine group by Boc-anhydride, which is covalent under the reaction conditions, in IPA/water with KOH acting as the catalyst as shown in Scheme 1.

This reaction was chosen because of its biphasic nature, which requires good mixing to facilitate mass transfer (for which SMV elements are particularly suitable<sup>7</sup>), and also because of heat-transfer related issues in semibatch mode due to the high reaction exotherm of  $-213$  kJ/mol A, which gave rise to thermally induced impurities. These impurities were mainly dimers of the starting material as shown in Scheme 1. The experimental procedure was as follows:

A solution of A in aqueous 2-propanol mixed with Boc-anhydride was stored in one feed tank under nitrogen, while a solution of 30% w/w potassium hydroxide in water was stored in the other. Both tanks were cooled to  $-5$  °C, and then the reactants were fed via the pumps into the static mixer, which had a pre-set jacket temperature of, for example,  $-20$  °C. The mixture exiting the reactor was then quenched into a stirred collection tank containing acetic acid, demineralised water, and IPA. Process samples were taken once steady state was reached, and conversion of A to B and C was determined via HPLC assay. Temperature distribution was also recorded over the length of the static

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**Table 3. Operating conditions and experimental results**

jacket temperature [°C]	mean reactor temperature [°C]	residence time [min]	ratio of KOH to A [–]	$c_{\text{base}}$ [mol/L]	conversion of A [%]	yield of B [%]	selectivity A to B [%]
–20	–10.2	4.8	5.4	1.45	94.5	94.4	98.4
–23.1	–15.5	13	5.4	1.33	96.0	95.9	99.9
–15	–8.4	13	5.4	1.33	92.2	92.1	99.9

mixer at three points (in the centre of the first mixing element at the reactor inlet at mid-height, and at the outlet point), to study the effect of the reaction exotherm. An increase in the temperature at the reactor inlet by 5 °C could be observed, but then the temperature only varied slightly between  $\pm 0.5$  °C at mid-length and at the exit point, indicating good temperature control and near isothermal behaviour.

Experiments were carried out by varying parameters known to have an influence on reaction selectivity, such as temperature, residence time, and stoichiometric ratio. Table 3 describes a representative selection of operating parameters and results.

Highest conversion using the static mixer reactor was achieved at low flow rate and low temperature, which is to be expected, as the reaction is exothermic.

At higher temperatures, formation of impurities as well as lower conversion was observed. In comparison to the batch process, which achieves 98% conversion, a slightly reduced degree of conversion was obtained. This is due to the limitations of the feed pumps and the reactor size, giving a maximum residence time of 13 min for the tubular reactor compared to a batch time of about 4 h on a 1 m<sup>3</sup> scale. Increasing the residence time, through enhancing reactor length, would be expected to further improve conversion.

The main advantage of operating this process in continuous mode was the reduction of dimer impurity levels in the reacted mixture by one order of magnitude in comparison to batch results, achieving a product selectivity of 99.9 versus 97% in semibatch mode. These impurities were known to rise with extended exposure to the alkaline reaction mixture and increased reaction temperature. On occasion they have even reached levels in prepared batches where crystallisation of the product has been hindered. These adverse conditions can be elegantly avoided in continuous mode, which features superior control over degree of mixing, uniformity of bulk temperature, and reaction mixture residence time. For the optimised operating conditions of –15 °C, 13 min residence time and 5.4 mol equiv of KOH to A, a production capacity of 0.4 kg B/h on the lab scale IPFR was calculated.

**Kinetics.** Kinetic parameters of the reaction were approximated by a simple first-order reaction with respect to the base concentration and matching conversion with residence time. The dimer side reaction could now be safely excluded from the model, as formation was only at insignificant concentration levels of below 0.1%.

The reaction mechanism was, therefore, simplified to:



The conversion ratio  $X/t_m$  was estimated from the experimental data obtained, which was used with the design

**Table 4. Kinetic parameters**

kinetic rate law	$r = k_0 \cdot \exp(-E/RT) \cdot c_{\text{base}}$	
activation energy $E$	[kJ/mol]	43.8
frequency factor $k_0$	[s <sup>-1</sup> ]	900000

equation for continuous reactors<sup>14</sup> to estimate specific reaction rate (eq F).

$$r = -c_{A,i} \frac{X}{t_m} \quad (\text{F})$$

For this comparatively fast reaction, the kinetic rate law was assumed to be of first-order with respect to the pseudohomogeneous base concentration  $c_{\text{base}}$ , which requires the complete mixing of both phases. We are aware of the fact that this model is comparatively crude and ignores mass-transfer steps. However, when considering the efficiency of the mixing elements for liquid/liquid systems,<sup>7</sup> we considered it justified to infer kinetic limitation. The kinetic rate law and the associated parameters are listed in Table 4.

As only a relatively narrow temperature range was investigated, these kinetics represent a rough approximation of the true values and should be used with caution. Also, the parameters were fitted to an integral reactor model as the concentration profile along its length could not be measured. They are, therefore, strictly only valid for the high range of conversion investigated. However, they proved to be accurate enough to simulate the approximate process behaviour in batch mode at manufacturing scale. This clearly highlighted that continuous processing was the method of choice for this chemistry as heat-transfer limitations of a stirred tank reactor would lead to extended addition and cycle times, reducing plant productivity.

## Conclusions

Our investigation showed that intensified plug flow reactors (IPFRs) hold promise for the synthesis of pharmaceuticals. The built rig revealed near ideal plug-flow behaviour and also good heat transfer, which lead to process improvements in the investigated chemical reaction in comparison to semi-batch operating mode. The calculated production capacity of the lab-size rig further demonstrates the potential of process intensified equipment. The reactor also proved to be a useful tool for the estimation of kinetic parameters, which are essential requirements for any follow up reactor design and process optimisation studies. As clear benefits were demonstrated, further investigations into this area will be undertaken.

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## NOMENCLATURE

$A$	area of the inside jacket wall ( $\text{m}^2$ )	$F(t)$	normalised conductivity (—)
$Bo$	Bodenstein number (—)	$k_0$	frequency factor ( $\text{s}^{-1}$ )
$c$	concentration, index A for compound A, index base for KOH, index $i$ for inlet ( $\text{kmol}/\text{m}^3$ )	$\dot{m}$	process fluid mass flow-rate ( $\text{kg}/\text{s}$ )
$C_p$	specific heat capacity ( $\text{J}/\text{kg}, \text{K}$ )	$N$	number of back-mixed tanks in cascade (—)
$\Delta T_{\text{mln}}$	mean logarithmic temperature difference ( $^{\circ}\text{C}$ or $\text{K}$ )	$r$	reaction rate ( $\text{kmol}/\text{m}^3, \text{s}$ )
$E$	activation energy ( $\text{kJ}/\text{mol}$ )	$Re$	Reynolds number (—)
$E(t)$	residence time distribution (—)	$t_m$	mean residence time ( $\text{s}$ )
		$\tau$	ideal space time ( $\text{s}$ )
		$T$	temperature, index i for inlet, o for outlet, f for process fluid, j for jacket ( $^{\circ}\text{C}$ or $\text{K}$ )
		$U$	overall heat transfer coefficient ( $\text{W}/\text{m}^2, \text{K}$ )
		$X$	degree of conversion of reactant A (—)

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