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Kinetic-free sizing criterion for the thermally controlled scale-up of batch fine-chemical processes

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ABSTRACT

A number of newly developed exothermic reactions of the fine-chemical industry can be safely tested at the industrial scale in an existing batch reactor since they cannot lead to dangerous reactor overpressures even under adiabatic conditions. However, when the process is scaled from a laboratory to an industrial reactor, the normal decrease of the heat transfer efficiency per unit volume can be so relevant that at the industrial scale the process cannot be thermally controlled, leading to a lower and less reproducible quality of the final product. In these cases, the industrial reactor must be equipped with an external heat transfer surface in addition to that provided by the reactor jacket only. The sizing of such an additional surface through conventional tools requires the knowledge of the heat release rate in the recommended temperature range and hence of the system kinetic behavior, which is often a missing information in the fine-chemical industry due to the fragmentation of the involved processes. In this work, a kinetic-free sizing criterion is presented for the temperature-controlled scale-up of intrinsically safe exothermic reactions carried out in the batch mode of operation, allowing for a simple and general estimation of the required heat transfer surface at the industrial scale from the analysis of the pseudo-adiabatic temperature trends measured during the original industrial batches. The proposed methodology has been validated using a set of process information about the final nitration step for the synthesis of an API as well as industrial-scale data collected during the scale-up of a water-in-oil emulsion polymerization for the synthesis of a polycationic thickener used in the cosmetic industry.

1. Introduction

In the fine chemical industry, an existing reactor is often used in its lifetime for performing several reactions, in a multipurpose logic [1,2].

When a newly developed process is exothermic, its scale-up to the industrial plant must be carefully evaluated in order to prevent first of all safety issues [3]. This because if the reaction heat evolution incomparably exceeds the available heat removal efficiency, dangerous overpressures can build-up in the reaction vessel, due to the volatility or to the thermal instability of the reaction mass above a threshold temperature [4]. In these cases, the process is normally developed since from the laboratory scale in the semibatch mode of operation, that is, by limiting the conversion rate and the related heat effects through the slow dosing of one reactant [3]. This allows for a smoother release of the reaction heat and for a prompt reactor shutdown at any time by interrupting the coreactant feed.

In general, exothermic processes carried out both in batch reactors (BR) and semibatch reactors (SBR) can be thermally controlled if the reaction heat is removed at a much lower time scale than that at which it is evolved [5]: this corresponds to a not-sensitive reactor regime with a pseudo-isothermal temperature behavior, characterized by relatively low and late temperature peaks. If, instead, the heat release rate is excessive when compared to the heat removal rate, the reactor regime becomes pseudo-adiabatic and sensitive, with an uncontrolled temperature behavior characterized by relatively high and early peaks [5–7].

The process safety literature of the last decades provides a number of safety criteria for discontinuous reactors (e.g., [8]). In particular, most of these safety criteria refer to SBRs, where potentially runaway reactions are normally performed [9–13], and they are based on the knowledge of the system kinetic behavior, at least in terms of an apparent dependence of the reaction rate on temperature and concentrations. This because the target reactor conditions are identified directly comparing the characteristic time at which the reaction heat is evolved to that at which it is removed through the reactor cooling system.

However, when dealing with fine chemical reactions, a detailed kinetic characterization or at least a deep reaction calorimetry study of the

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Nomenclature

A	heat transfer surface, m^2
A	pre-exponential factor (suitable units)
API	active pharmaceutical ingredient
B	$= \Delta T_{ad} E/RT^2$, thermal reaction number, –
C	molar concentration, $kmol/m^3$
$\widehat{C}_P$	mass heat capacity at constant pressure, kJ/(kg·K)
Da	$= \left(\nu_{lr}/C_{lr,0}\right) \times r^{eff} \times t_R$, Damköhler number, –
exc	molar excess of a reactant, –
E	activation energy, kJ/kmol
F_t	$= \exp\left[\frac{E_{app}}{R}\left(\frac{1}{T_{PA}} - \frac{1}{\overline{\overline{T}}_{PI}}\right)\right]$, –
m	mass, kg
$\dot{M}$	mass flow rate, kg/s
n	number of moles, kmol
$\dot{Q}$	heat duty, kW or kcal/h (where specified)
$\widehat{\dot{Q}}$	dimensionless heat duty, –
r	reaction rate, $kmol/(m^3 \cdot s)$
r	ratio, in the expression of r_{UA}, –
R	gas constant, =8.314 kJ/(kmol K)
S	parametric sensitivity coefficient, –
St	$= UA\, t_R/m\widehat{C}_P$, Stanton number, –
t	time, s (or other units, where specified)
T	temperature, °C or K
$\widehat{T}$	dimensionless temperature, –
ΔT_{ad}	$= \frac{n_{lr,0}/\nu_{lr}\left(-\Delta\widetilde{H}_r\right)}{m\widehat{C}_P}$, adiabatic temperature rise, °C
ΔT_{cool}	$= T_{cool} - T_{cool}^{IN}$, coolant temperature rise, °C
U	overall heat transfer coefficient, $kW/(m^2K)$
V	volume, m^3

Subscripts and superscripts

ad	adiabatic
app	apparent
UA	subscript in the expression of r_{UA}
cool	coolant
eff	effective
ext	external
FAM	N-(2-phenoxypnenyl) methane sulfonamide
IN	inlet
j	j-th time
jkt	jacket
lr	limiting reactant
NIM	N-(4-nitro, 2-phenoxypnenyl) methane sulfonamide
OUT	outlet
PA	pseudo-adiabatic
PI	pseudo-isothermal
r	reaction
R	reference
tot	total
0	initial

Greek symbols

$\Delta\widetilde{H}$	reaction enthalpy, kJ/kmol
ΔT	temperature rise or difference, °C
ν	stoichiometric coefficient, –
τ	dimensionless time, –
X	conversion, –
Ψ	Ψ number, -

system is often missing because of the intrinsic mismatch between the time and the resources needed to perform them and the level of process fragmentation to be managed [14]. For this reason, in the last years kinetic-free approaches have been developed for identifying and on-going assessing the safe behavior of both BRs and SBRs, based on a comparison between the measured energy release rate of the system and an expected target one [15–22]. Such approaches are useful for both identifying safe conditions as well as for monitoring them, hence effectively minimizing the frequency of occurrence of runaway phenomena at the industrial scale.

Even when dangerous overpressures cannot build-up in the reaction vessel, as for exothermic reaction processes belonging to the first and second categories of Stoessel's classification [23], an effective control of the reaction temperature and hence of the average reaction rate can be crucial for stabilizing the quality of the products. Such a thermal control is normally not an issue at the laboratory scale because of the intrinsically high ratio between the heat transfer surface and the reaction volume. However, when moving from the laboratory to the industrial scale this ratio undergoes a significant drop, roughly proportional to the ratio of the industrial to laboratory-scale vessel diameters [3]. If such a parameter is well below the minimum threshold to guarantee an effective temperature control, the resulting behavior of the system becomes pseudo-adiabatic at the industrial scale, with excessive and early temperature peaks. In these cases, the reactor must be equipped with an additional heat transfer surface, typically consisting in an external heat exchanger installed on a recycle loop [24].

This is a typical design problem, which requires the knowledge of the heat evolution rate of the chemical process in the temperature range of interest [25]; in other words, the kinetics of the chemical processes must be investigated, at least using calorimetric equipment. If the kinetics of the process is unknown, an oversimplified approach requires enforcing at the industrial scale the same ratio of the heat transfer surface to the reaction volume characterizing the laboratory reactor. However, usually this oversimplified approach is not useful in the industrial practice since it leads to unrealistic overestimations of the additional heat transfer surface. This because the heat exchange surface to reaction volume ratio available at the lab-scale normally largely exceeds the minimum value required.

Reviews of scale-up criteria for specific processes are available (e.g., microwave-assisted processes [26]; industrial fermentation processes [27]; sonic-assisted processes [28]), but a general kinetic-free sizing criterion for generic exothermic chemical processes unable to generate dangerous overpressures carried out in batch reactors is still unavailable in the Authors' knowledge.

In this work, a simple sizing criterion is proposed, allowing for an easy estimation of a reasonable additional heat removal surface of an industrial batch reactor in which an exothermic reaction (unable to generate dangerous overpressures) must be performed under temperature-controlled conditions.

It is worth stressing that the proposed criterion is not aimed to find the optimal (that is, the minimum) additional heat transfer surface able to guarantee pseudo-isothermal conditions since, when an additional heat transfer surface is required for a given process carried out in a multipurpose batch reactor, such an additional heat transfer surface is usually provided by an available equipment and not by a new designed one. Therefore, as previously mentioned, the proposed criterion just aims to provide a reasonable estimation of the required additional heat transfer surface without requiring any kinetic information as well as avoiding an excessive oversizing.

The proposed criterion is based on the analysis of pseudo-adiabatic temperature trends measured on the industrial-scale reactor, requiring neither a deep calorimetric investigation nor a kinetic characterization of the chemical reaction. It must be stressed that a preliminary calorimetric investigation is mandatory whenever the process to be scaled-up can develop dangerous overtemperatures (and therefore overpressures) under adiabatic conditions [3].

The criterion has been validated through a set of process information and industrial data concerning two processes: the final nitration step for the synthesis of an anti-inflammatory and the water-in-oil emulsion polymerization for producing a polycationic thickener used in cosmetic applications [29], the performance of which is strongly affected, among the others, by the temperature profile during the polymerization.

2. Sizing criterion

In order to develop a kinetic-free sizing criterion for the thermally controlled scale-up of an exothermic batch process, the mathematical model of the reactor has been recast in a suitable form, allowing for deriving a set of easy-to-measure parameters, from which the required heat removal area can be estimated on the basis of available process data.

The macroscopic energy balance for a batch reactor states that:

$$m\widehat{C}_P\frac{dT}{dt} = r^{eff}V\left(-\Delta\widetilde{H}_r\right) - UA(T - T_{cool}) = \dot{Q}_r - \dot{Q}_{cool} \tag{1}$$

r^{eff} being the macrokinetic reaction rate, accounting for potential mass transfer limitations.

Defining $\Psi = 100\dot{Q}_{cool}/\dot{Q}_r$ as the percentage ratio of the heat evolution rate that is instantaneously removed through the cooling system [5], and indirectly estimating $\dot{Q}_r$ in terms of the measured heating rate, $dT/dt \approx \Delta T/\Delta t$, through equation (1), the following expression of Ψ can be derived:

$$\Psi = \frac{100}{1 + \frac{m\widehat{C}_P dT/dt}{UA(T - T_{cool})}} \tag{2}$$

Recording at a suitable time frequency the temperature and flow rate values of a batch carried out in the industrial-scale reactor from the reaction onset up to the temperature peak, and considering that the $\dot{Q}_{cool}$ value can be estimated through the temperature increase of the coolant through the relation $\dot{Q}_{cool} = UA(T - T_{cool}) \approx \dot{M}_{cool}\widehat{C}_{P,cool}\Delta T_{cool}$ [15], the Ψ value at time t_j, Ψ_j, can be calculated as:

$$\Psi_j \approx \frac{100}{1 + \frac{m\widehat{C}_P\left(T_j - T_{j-1}\right)/\left(t_j - t_{j-1}\right)}{UA\left(T_j - T_{cool,j}\right)}} \approx \frac{100}{1 + \frac{m\widehat{C}_P\left(T_j - T_{j-1}\right)/\left(t_j - t_{j-1}\right)}{\dot{M}_{cool,j}\widehat{C}_{P,cool}\Delta T_{cool,j}}} \tag{3}$$

It is worth noticing that a sufficiently wide sampling of the plant variables (i.e., reactor temperature; inlet and outlet coolant temperature; coolant flow rate) is required to keep a satisfactory accuracy.

Asymptotically, a fully pseudo-isothermal regime of the reactor corresponds to a Ψ value approaching 100, being $\dot{Q}_r \approx \dot{Q}_{cool}$ at any instant; a fully adiabatic regime corresponds instead to a Ψ value close to 0, since in this case $\dot{Q}_{cool} \approx 0$ [5]. However, for a practical use of this criterion a threshold value for Ψ must be defined, above which the reactor regime can be classified as temperature-controlled. As an order of magnitude, 50 can be considered a reasonable discriminating Ψ value in most of the industrial cases of practical interest [5]. Note that such a threshold value, even if arising from realistic process assumptions, is affected by an unavoidable degree of arbitrariness.

A more general and evident separation between the two reactor regimes can be defined combining the energy approach based on the Ψ parameter with a Semenov-like representation of the results. To this aim, the macroscopic energy balance (1) can be recast in dimensionless form as follows:

$$\frac{d\widehat{T}}{d\tau} = \Delta\widehat{T}_{ad}Da - St\left(\widehat{T} - \widehat{T}_{cool}\right) = \dot{\widehat{Q}}_r - \dot{\widehat{Q}}_{cool} \tag{4}$$

where $\Delta\widehat{T}_{ad} = \left[\left(-\Delta\widetilde{H}_r\right)n_{lr,0}/\nu_{lr}\right]/(m\widehat{C}_P T_R)$ is the dimensionless adiabatic temperature rise, $Da = \left(\nu_{lr}/C_{lr,0}\right)r^{eff}\,t_R$ is the instantaneous Damköler number and $St = UA\,t_R\,/(m\widehat{C}_P)$ is the Stanton number. Combining the definition of Ψ with the expressions of $\dot{\widehat{Q}}_r$ and $\dot{\widehat{Q}}_{cool}$ in equation (4), the following relationship between Ψ and St/Da can be derived:

$$\frac{St}{Da} = \frac{\Delta T_{ad}}{T - T_{cool}}\frac{\Psi}{100} \tag{5}$$

Once known the ΔT_{ad} value, the St/Da ratio can be computed at any time t_j from the measured values of the various temperatures and flow rate on the industrial-scale reactor.

Deriving equation (4) in time and considering that $r = A\exp\left(-E_{app}/RT\right)f(\overline{C})$, the expression of d^2T/dt^2 becomes:

$$\frac{d^2T}{dt^2} = (B\,Da - St)\frac{dT}{dt}\frac{1}{t_R} \tag{6}$$

where $B = E_{app}\Delta T_{ad}/(RT^2)$ is the thermal reaction number.

A positive value of the second order temperature–time derivative from the reaction onset to the temperature peak is related to a pseudo-adiabatic and sensitive reactor behaviour. Since in this time range dT/dt is positive, the reactor regime is thermally controlled and non-sensitive if (at least for the larger part of such a time range):

$$\frac{St}{Da} \geq B \rightarrow B\frac{Da}{St} \leq 1 \tag{7}$$

The only kinetic parameter required by this criterion is the apparent activation energy. However, the additional heat removal surface estimated through the following criterion is poorly sensitive to the E_{app}/R value, so that an order of magnitude estimation suffices. A higher E_{app}/R value corresponds to a higher dependence of the reaction rate on temperature, requiring a higher heat removal area to counteract the temperature self-acceleration. However, at a higher E_{app}/R value a lower reaction rate also corresponds, for a given conversion and temperature, which, instead, makes a lower heat removal area sufficient. Such an opposite tendency physically explains the reason of the relatively low sensitivity of the proposed sizing criterion to E_{app}/R, hence preserving its kinetic-free nature.

Moreover, for most organic reactions of practical interest, E_{app}/R ranges from 5000 to 10000 K [3]: therefore, in the absence of relevant mass transfer limitations a value closer to 10000 K can be assumed, whereas for diffusion-controlled systems a value closer to 5000 K can be more realistic.

For the sake of example, some industrial data about a solvent-based polymerization of acrylic acid taken from the literature [5] have been recast trough equation (5) in terms of B Da/St and plotted in Fig. 1. An E_{app}/R value equal to 5000 K has been assumed in this case since the monomer has to diffuse towards the polymer particles where it reacts with the living polymer chains, hence increasing the dimension of the polymer particles and the amount of the polymeric phase itself. Being the polymerization reaction of the acrylic monomer typically a fast reaction, the diffusion of the monomer easily becomes the limiting phenomenon, and the reaction usually occurs in a thin external shell.

Four sets of data are plotted, corresponding to a normal reactor operation (labelled with 1 in Fig. 1) and to three upset conditions (labelled with S1, S2, and S3 in Fig. 1), A clear qualitative difference between the pseudo-isothermal regime and the three pseudo-adiabatic ones is evident.

Note that the requirement of equation (7) should be used as an order of magnitude criterion, that is, regimes characterized by values of B Da/

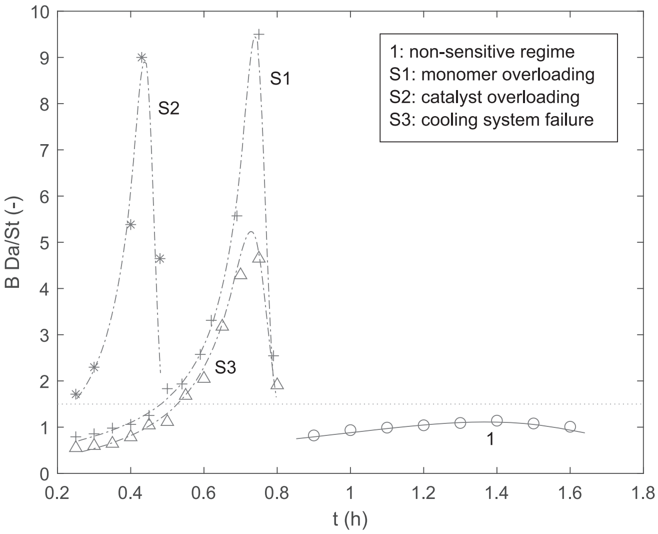


Fig. 1. Industrial batch polymerization of acrylic acid. Experimental data from [5] recast in terms of B Da/St values.

St steadily close or lower than 10^0 as an order of magnitude can be classified as poorly sensitive and hence acceptable at the industrial scale. Coherently, we can see from Fig. 1 that the pseudo-isothermal run 1 involves B Da/St values steadily close to the order of magnitude of 10^0, while the B Da/St values for the pseudo-adiabatic runs S1, S2, and S3 sharply increase towards to the order of magnitude of 10^1.

When scaling-up an exothermic batch process, the chemical recipe typically provides information about the initial reaction temperature and the maximum temperature value that can be allowed (the so-called MAT, Maximum Allowable Temperature). Considering that when scaling-up from the laboratory to the industrial scale the heat removal surface per unit reaction volume decreases roughly as the ratio of the industrial to the laboratory reactor diameters, an exothermic reaction process that can be thermally controlled at the laboratory scale might undergo a pseudo-adiabatic behaviour once implemented in an existing industrial reactor [3].

If the system cannot lead even under adiabatic conditions to potentially dangerous overpressures, as for reaction processes belonging to the first two categories of Stoessel's classification of exothermic reactions [23], the scale-up does not imply relevant safety issues from this point of view, so that the process can be carried out at the industrial scale even without a deep preliminary calorimetric study apart from that required to estimate the ΔT_{ad} value. However, an uncontrolled temperature trend at the industrial-scale reactor can lead to temperature values higher than those allowed by the chemical recipe, with negative consequences on the product quality. Moreover, a pseudo-adiabatic behaviour corresponds also to a sensitive operating regime of the reactor, which makes the process conditions and hence the product quality poorly reproducible from batch to batch [5].

Under thermally controlled conditions, $\frac{d\widehat{T}}{d\tau} \approx 0$ and equation (4) simplifies to:

$$\overline{T}_{PI} = T_{cool} + 1.05\frac{Da}{St}\Delta T_{ad} \tag{8}$$

where $\overline{T}_{PI}$ is an estimation of the reactor temperature under psudo-isothermal conditions and the factor 1.05 accounts for any displacement between ideal pseudo-isothermal conditions and their practical approximation [9–11].

Setting $\overline{T}_{PI}$ in equation (8) equal to the average value of the temperature range recommended by the chemical recipe, the corresponding St/Da value allowing to perform the reaction under thermally controlled conditions at the industrial scale can be estimated from this equation.

However, also the constraint B Da/St ≤ 1 (as an order of magnitude) must be fulfilled. To account for the order of magnitude estimation, the threshold value for the B Da/St can be set equal to $1.5 = 3/2$ instead of 1, as previously discussed for axial-flow reactors [30]. Note that this threshold involves some degree of arbitrariness; other values, always of the order of magnitude 10^0, could be used.

Therefore, since this last constraint requires St/Da value higher or equal to (2/3) B (calculated at $\overline{T}_{PI}$), if the estimated St/Da is lower than (2/3) B, the required St/Da must be set equal to (2/3) B and the reaction can be performed in the industrial-scale reactor under thermally controlled conditions at an average temperature closer to the initial temperature stated by the chemical recipe.

Moreover, being the process intrinsically safe as proved by the ΔT_{ad} value preliminary measured, it is possible to run it in the industrial-scale reactor without worrying about possible dangerous pressurization of the reactor. During such preliminary runs in an existing industrial-scale batch reactor, the time trends of the reaction temperature as well as that of the coolant flow rate and of the inlet/outlet coolant temperatures can be measured at a suitable time frequency. If the system undergoes a pseudo-adiabatic behaviour due to an insufficient heat removal surface, the quality of the product cannot be guaranteed. However, the measurements carried out during a few reaction batches can be averaged to generate a representative picture of pseudo-adiabatic conditions, therefore smoothing uncontrolled local deviations from batch to batch.

These measured data can be used to calculate a calorimetric conversion trend as:

$$X = \frac{(m\widehat{C}_P)(T - T_0) + \int_0^t \left(\dot{M}_{cool}\widehat{C}_{P,cool}\Delta T_{cool}\right)dt}{\frac{n_{lr,0}}{\nu_{lr}}\left(-\Delta\widetilde{H}_r\right)}100 \tag{9}$$

The reactor temperature vs. conversion trends under pseudo-adiabatic and pseudo-isothermal conditions are quite different, since the latter one is quite close to $\overline{T}_{PI}$ for almost all the conversion range. From the temperatures and flow rate measurement on the industrial-scale reactor operating in the pseudo-adiabatic regime it is straightforward calculating the trends of Ψ and St/Da from the reaction onset to the peak conditions, where a nearly quantitative conversion is expected.

From the St/Da values under the actual pseudo-adiabatic conditions ($St/Da|_{PA}$) and the target pseudo-isothermal ones ($St/Da|_{PI}$) computed at each conversion value, the following relationship between the available heat transfer surface of the industrial-scale reactor $(UA)_{jkt}$ and the external heat transfer surface $(UA)_{ext}$ to be installed for managing the process under pseudo-isothermal conditions at $\overline{T}_{PI}$ can be derived:

$$\frac{(UA)_{ext}}{(UA)_{jkt}} \simeq \frac{St/Da|_{PI}}{St/Da|_{PA}}\exp\left[\frac{E_{app}}{R}\left(\frac{1}{T_{PA}} - \frac{1}{\overline{T}_{PI}}\right)\right] - 1 \tag{10}$$

where T_{PA} is the measured reactor temperature under pseudo-adiabatic conditions at different times. For a practical use of equation (10), it is worth noticing that the overall heat transfer coefficients through the original reactor jacket and an external shell-and-tube heat exchanger are normally close to each other. If instead of a shell-and-tube heat exchanger an additional plate-type heat exchanger is installed, a 4 times higher heat transfer coefficient is normally expected for the external heat exchanger [31].

Equation (10) provides different values of $(UA)_{ext}$ in time. Conservatively, the value computed at the peak dT/dt conditions, roughly corresponding also to the peak of the reaction rate under pseudo-adiabatic conditions, can be used. To prevent an excessive oversizing of the additional heat transfer surface, the required St/Da value could be calculated through equation (8) using the minimum available coolant temperature in the plant instead of the jacket-average value.

Equation (10) states that at T_{PA} values higher than $\overline{T}_{PI}$ the (UA) value increase from pseudo-adiabatic to pseudo-isothermal conditions is less than proportional to the ratio of the two corresponding St/Da values, being mitigated by the factor $F_t = \exp\left[\frac{E_{app}}{R}\left(\frac{1}{T_{PA}} - \frac{1}{\overline{T}_{PI}}\right)\right] < 1$. This factor accounts for the decrease of the average reaction rate due to the lower average reaction temperatures: as an order of magnitude, for typical E_{app}/R values a doubling of the reaction rate is expected every 10 K temperature increase [3].

The step-by-step procedure for the application of the proposed scale-up criterion is summarized through the flow chart of Fig. 2.

As anticipated above, the sensitivity of the heat transfer efficiency estimated through equation (10) to the assumed E_{app}/R value is relatively low for realistic process parameters, which is of particular importance for preserving the kinetic-free nature of the proposed criterion. A parametric sensitivity coefficient of the overall heat transfer surface to the assumed E value can be defined as:

$$S_{(UA)_{tot}/E_{app}} = \frac{E_{app}}{|\Delta E_{app}|}\frac{|\Delta(UA)_{tot}|}{(UA)_{tot}} = \frac{E_{app}}{|\Delta E_{app}|}|r_{UA} - 1| \tag{11}$$

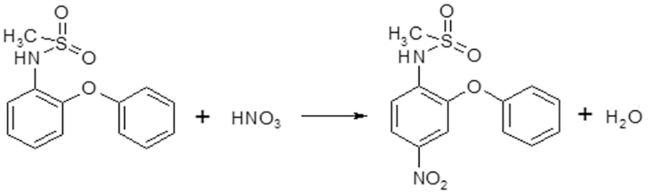
where ΔE_{app} is the change in the apparent activation energy and $\Delta(UA)_{tot}$ is the corresponding change in the estimated $(UA)_{tot}$ value. Considering a $\overline{T}_{PI}$ range of industrial interest (e.g., from 40 to 100 °C), the sensitivity coefficient values resulting from typical E_{app}/R values [3] estimated with a ± 20 % uncertainty and for $T_{PA} - \overline{T}_{PI}$ differences up to 20 °C are always lower than one, which means that any approximations on the E_{app}/R value is reduced when used to estimate the heat removal surface required for pseudo-isothermal process conditions. Moreover, such approximations in the estimation of the external heat exchange area are typically included in the usual oversizing of the effective heat transfer surface due to the selection of a standard equipment [31].

3. Case-study

The proposed criterion has been validated through industrial-scale data and process information corresponding to two industrial processes, taken from the pharmaceutical and fine-chemical industry, respectively. The two selected processes are fairly different in terms of reaction class and system heterogeneity: this, in order to test the degree of generality of the proposed criterion, derived in any case from universal mass and energy balance statements for a batch reactor, without any a-priori assumption potentially valid for a particular class of chemical reactions.

3.1. Nitration reaction for producing an API

The first case study corresponds to the nitration of a pharmaceutical intermediate (that is, N-(2-phenoxypnenyl) methane sulfonamide, in the following referred to as FAM) performed through aqueous nitric acid in homogeneous phase, using acetic acid as a solvent:



(12)

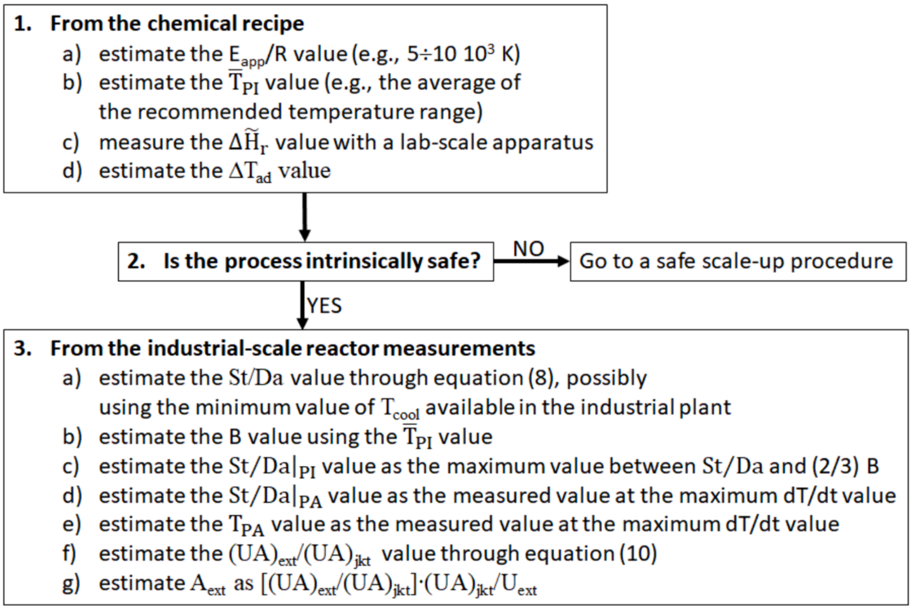
The reaction, widely described in the process safety and intensification literature [32–34], generates an API (that is, N-(4-nitro, 2-phenoxypnenyl) methane sulfonamide, in the following referred to as NIM), widely used in the past as a non-steroidal anti-inflammatory known as NIMESULIDE®.

The reaction has to be performed at the industrial scale in a 5 m^3 batch reactor with a 12 m^2 heat transfer surface provided by a cooling jacket with water at a minimum temperature of 25 °C and an overall heat transfer coefficient equal to about 0.29 kW/m^2K; cooling water temperature is increased up to 40 °C at the beginning to start the reaction and after the exothermic peak to keep the reaction temperature in the recommended 40 ÷ 45 °C range, whereas in the middle a 30 °C coolant temperature is adopted, to face the reaction heat evolution.

This process has been thoroughly investigated in the literature [32–34], where a reliable kinetic characterization of the system is also provided. This allows for using simulated data as a reliable proxy of the experimental ones for quickly validating the estimation of the additional heat transfer surface performed through the kinetic-free criterion presented in this paper.

The macroscopic mass and energy balances of an industrial batch reactor can be written as:

$$\frac{d(X/100)}{dt} = r/C_{FAM,0} \tag{13}$$



1. **From the chemical recipe**
   a) estimate the E_{app}/R value (e.g., 5÷10 10^3 K)
   b) estimate the $\overline{T}_{PI}$ value (e.g., the average of the recommended temperature range)
   c) measure the $\Delta\widetilde{H}_r$ value with a lab-scale apparatus
   d) estimate the ΔT_{ad} value

2. **Is the process intrinsically safe?**

NO → Go to a safe scale-up procedure

YES

3. **From the industrial-scale reactor measurements**
   a) estimate the St/Da value through equation (8), possibly using the minimum value of T_{cool} available in the industrial plant
   b) estimate the B value using the $\overline{T}_{PI}$ value
   c) estimate the $St/Da|_{PI}$ value as the maximum value between St/Da and (2/3) B
   d) estimate the $St/Da|_{PA}$ value as the measured value at the maximum dT/dt value
   e) estimate the T_{PA} value as the measured value at the maximum dT/dt value
   f) estimate the $(UA)_{ext}/(UA)_{jkt}$ value through equation (10)
   g) estimate A_{ext} as $[(UA)_{ext}/(UA)_{jkt}]\cdot(UA)_{jkt}/U_{ext}$

Fig. 2. Flow-chart for the thermally-controlled scale-up of intrinsically safe exothermic batch reaction processes.

$$\frac{dT}{dt} = \Delta T_{ad}\frac{d(X/100)}{dt} - \frac{(UA)_{jkt} + (UA)_{ext}}{m\widehat{C}_P}(T - T_{cool}) \tag{14}$$

where in this case: $r\left[\frac{kmol}{m^3 s}\right] = 1.001\times 10^{12}\exp\left(-\frac{85940\left[\frac{kJ}{kmol}\right]}{RT[K]}\right)\times \left(C_{HNO_3}\left[\frac{kmol}{m^3}\right]\right)^2\left(C_{FAM}\left[\frac{kmol}{m^3}\right]\right)^{0.2}$ and the reactants concentrations are related to the percentage conversion, X, through the expressions $C_{HNO_3} = C_{FAM,0}\left(exc - \frac{X}{100}\right)$ and $C_{FAM} = C_{FAM,0}\left(1 - \frac{X}{100}\right)$, $exc = 1.04$ being the stoichiometric excess of nitric acid equal to 4 %. Integrating equations (13) and (14) through the Matlab suite of programs with the initial conditions $X_0 = 0$ and $T_0 = 313.15$ K (that is, 40 °C), the conversion and temperature time profiles of Fig. 3 can be calculated (the industrial recipe involves about 3000 kg of acetic acid, 600 kg of FAM, and 220 kg of 65 % w/w nitric acid), showing that a too high temperature peak (close to 65 °C) is reached through the available heat transfer surface; this is well above the 40 ÷ 45 °C range recommended for preventing side reactions, such as multiple nitration.

As previously mentioned, to recover a pseudo-isothermal regime of the batch reactor in the accepted temperature range, the reactor can be equipped with an external heat exchanger [24,31], which size can be estimated through the criterion summarized in Fig. 2.

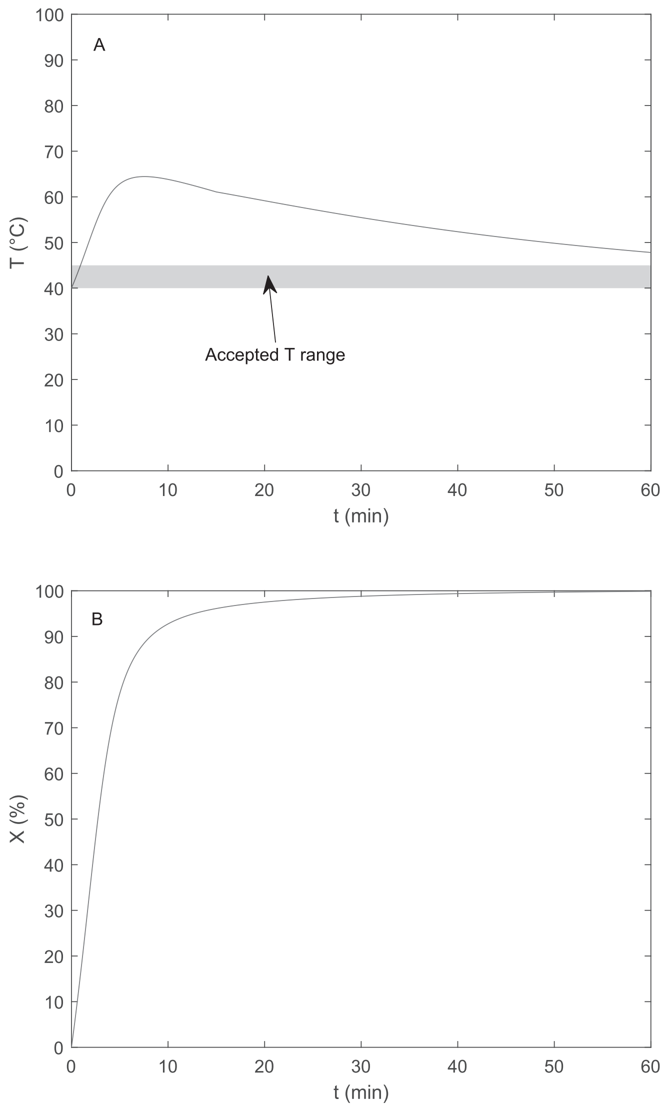


Fig. 3. Nitration of FAM to NIM in a 5 m^3 batch reactor equipped with a 12 m^2 cooling jacket. (A) reactor temperature vs. time; (B) conversion vs. time.

Step 1a of the flow chart of Fig. 2 requires an estimation of E_{app}/R. For almost all the organic reactions of industrial interest E_{app}/R ranges from 5000 to 10000 K [3], the lower limit being more typical of reaction systems in which diffusion resistances play a not negligible role, as for heterogeneous systems operating in the fast reaction regime. Moreover, organic chemistry textbooks (such as [35,36]) provide the activation energies of several classes of chemical reactions. In this case, being the system homogeneous, an E_{app}/R value close to 10000 K can be assumed, which agrees with the value from the expression of the reaction rate reported above, where an $E_{app}/R = 85940/8.314 = 10337$ K is involved.

Step 1b in Fig. 2 requires an estimation of $\overline{T}_{PI}$ as the average value of the recommended temperature range (in this case, 40 ÷ 45 °C); therefore, an average pseudo-isothermal temperature $\overline{T}_{PI} = 42.5$ °C can be estimated.

Step 1c in Fig. 2 involves the measurement of the reaction heat, which is equal to −127.4 kJ/mol; accounting for an average heat capacity of the mixture of 2.3 kJ/kg°C, an adiabatic temperature rise of about 33 °C can be estimated (step 1d of the flow chart of Fig. 2).

According to the aforementioned recipe, the process can be safely performed at the industrial scale even under test conditions without over-pressurization risks of the reactor since a maximum temperature of the synthesis reaction under adiabatic conditions lower than 80 °C can be computed. Such a MTSR value is well below both the atmospheric boiling point of the reaction mass (that is, 120 °C) and its experimentally determined decomposition temperature (that is, 210 °C [32]). Therefore, the step 2 of the flow chart of Fig. 2 allows for proceeding with the proposed methodology.

Using a minimum coolant temperature equal to $T_{cool} = 25$ °C, a value of St/Da equal to about 1.98 can be calculated through equation (8) (step 3a of the flow chart of Fig. 2).

Through the E_{app}/R value estimated above, a B value equal to about 3.4 can be then estimated (step 3b of the flow chart of Fig. 2). Finally, a value of $St/Da|_{PI} = \max\left(1.98; \frac{2}{3}3.4\right) = 2.28$ is selected (step 3c of the flow chart of Fig. 2).

Then, step 3d of the flow chart of Fig. 2 requires estimating Ψ and St/Da values under pseudo-adiabatic conditions through equations (3) and (5), in the time range from the reaction onset to the peak temperature conditions. At the time at which the maximum dT/dt was detected (in this case, just after the reaction triggering), the reactor temperature is roughly $T|_{PA}$ 50 °C (step 3e of the flow chart of Fig. 2), corresponding to a value of $St/Da|_{PA}$ equal to about 0.123.

A value of the ratio $(UA)_{ext}/(UA)_{jkt}$ equal to about 7.6 can be calculated through equation (10) (step 3f of the flow chart of Fig. 2), corresponding to an about 20 m^2 plate-type external heat exchanger (step 3 g of the flow chart of Fig. 2).

The stepwise results of the applied procedure are summarized in Table 1.

In Fig. 4 the calculated temperature and conversion trends for the 5 m^3 reactor equipped with a 20 m^2 recycle loop plate-type exchanger are plotted, zoomed again in the region around the temperature peak: it can be noticed that the reactor behaviour is now pseudo-isothermal, with temperature peaks close to 45 °C, as required by the chemical recipe.

The two reactor regimes (pseudo-adiabatic, PA, and pseudo-isothermal, PI) are compared in Fig. 5 in terms of B Da/St. Also in this case, the pseudo-isothermal conditions involve B Da/St values steadily close to the order of magnitude of 10^0, while the B Da/St values for the pseudo-adiabatic conditions sharply overcome the threshold order of magnitude of 10^1.

These calculations have been repeated through the same procedure accounting for a potential ± 20 % inaccuracy in the estimation of E_{app}/R. The resulting additional heat transfer surface is always reasonably

Table 1
Summary of the stepwise results for the nitration of FAM to NIM.

Pseudo-isothermal regime characterization			
Recipe T range	40 ÷ 45 °C	$\overline{T}_{PI}$	42.5 °C
Recipe amounts	600 kg FAM 3820.1 kg overall		
$\Delta\widetilde{H}_r$	−127.4 kJ/mol	ΔT_{ad}	33 °C
$\widehat{C}_P$	2.3 kJ/(kg°C)	$St/Da\|_{eq.\ 8}$	1.98
$T_{cool,MIN}$	25 °C	2/3B	2.28
E_{app}/R	10000 K	$St/Da\|_{PI}$	2.28
Pseudo-adiabatic measurements			
T profile	See Fig. 3A		
U_{jkt}	0.29 kW/(m^{2}K)	T_{PA}	50 °C
U_{ext}	1.16 kW/(m^{2}K)	$St/Da\|_{PA}$	0.123
Additional heat transfer surface estimation			
		$(UA)_{ext}/(UA)_{jkt}$	7.6
A_{jkt}	12 m^2	A_{ext}	23 m^2 (plate-type)

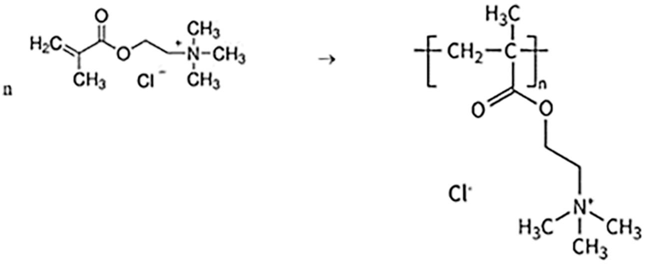
close to 20 m^2.

3.2. Acrylic emulsion polymerization

The second industrial case investigated to validate the proposed criterion is a water-in-oil emulsion polymerization of the fine chemical industry for the production of an acrylic polycationic thickener, used in a number of cosmetic applications [29].

In this case, a set of data collected from an industrial-scale batch reactor were available, corresponding to the reactor equipped with its jacket only and with an additional external plate-type heat exchanger, respectively. The latter equipment was selected among a list of spare equipment available in the plant. No kinetic information was in this case available, as normally occurs when dealing with fine chemical and pharma processes.

The polymerization of the involved water-soluble acrylic monomer occurs in the aqueous droplets dispersed in a paraffinic continuous phase, according to the reaction:



(15)

The process roughly consists in the preparation of a stable water-in-oil emulsion through the addition at room temperature of the aqueous phase to a paraffinic phase containing a suitable emulsifier. Once the emulsion has been generated, the exothermic polymerization usually self-triggers just heating the system at temperatures close to 50 °C. According to the chemical recipe, the polymerization should be better performed in the range 55 ÷ 60 °C, being the acceptable range a bit wider, that is, 50 ÷ 60 °C.

As the polymerization starts, the aqueous dispersed phase in which the crosslinked polymerization occurs undergoes a sudden viscosity increase, lowering the mobility of the living polymer chains and hence the rate of the termination reactions: this can lead to a self-accelerating temperature behaviour, characterized by early and excessive temperature peaks if the installed heat transfer surface of the reactor is insufficient.

The process was first implemented at the industrial scale in a 15 m^3 reactor with a 20.5 m^2 heat transfer surface. According to the chemical recipe, the scale-up could be safely performed without over-pressurization risks of the reactor and connected equipment since at the industrial-scale an adiabatic temperature rise of less than 40 °C can be estimated from laboratory-scale measurements (steps 1c and 1d of the flow chart of Fig. 2), to which a maximum temperature of the synthesis reaction under adiabatic conditions of about 90 °C corresponds. Since the atmospheric boiling point of the water/paraffin two-phase mixture in the reactor is close to 100 °C, no significant reactor over-pressures are expected and the process could be safely scaled-up (step 2 of the flow chart of Fig. 2).

The average conversion and temperature trends measured on the industrial-scale batches are plotted in Fig. 6, zoomed in the region around the temperature peak. It appears that the heat transfer surface per unit volume of the industrial reactor was insufficient, leading to temperature peaks close to 80 °C (that is, more than 20 °C above the MAT recommended by the chemical recipe), at which about 90 % of the monomer conversion was achieved. Under such conditions the rheology behaviour of the generated acrylic thickener is poorly reproducible and often characterized by a too low viscosities of the 0.5 % aqueous gel used for testing its quality, leading to a correspondingly unsatisfactory performance in the final application.

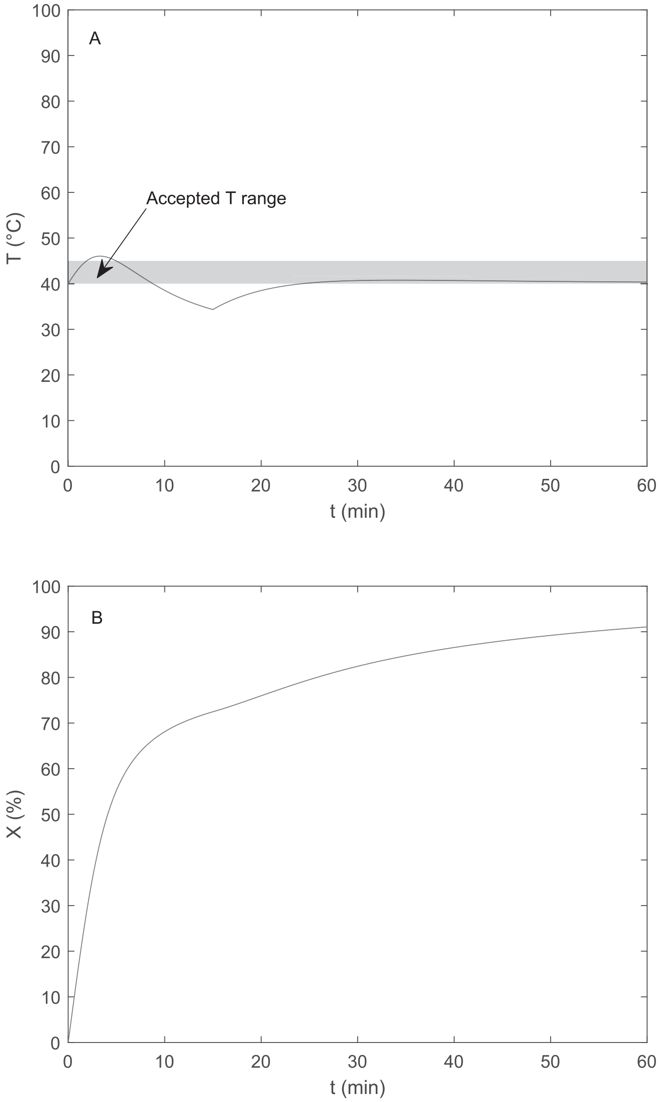


Fig. 4. Nitration of FAM to NIM in a 5 m^3 batch reactor equipped with a 12 m^2 cooling jacket and a 20 m^2 external plate-type heat exchanger. (A) reactor temperature vs. time; (B) conversion vs. time.

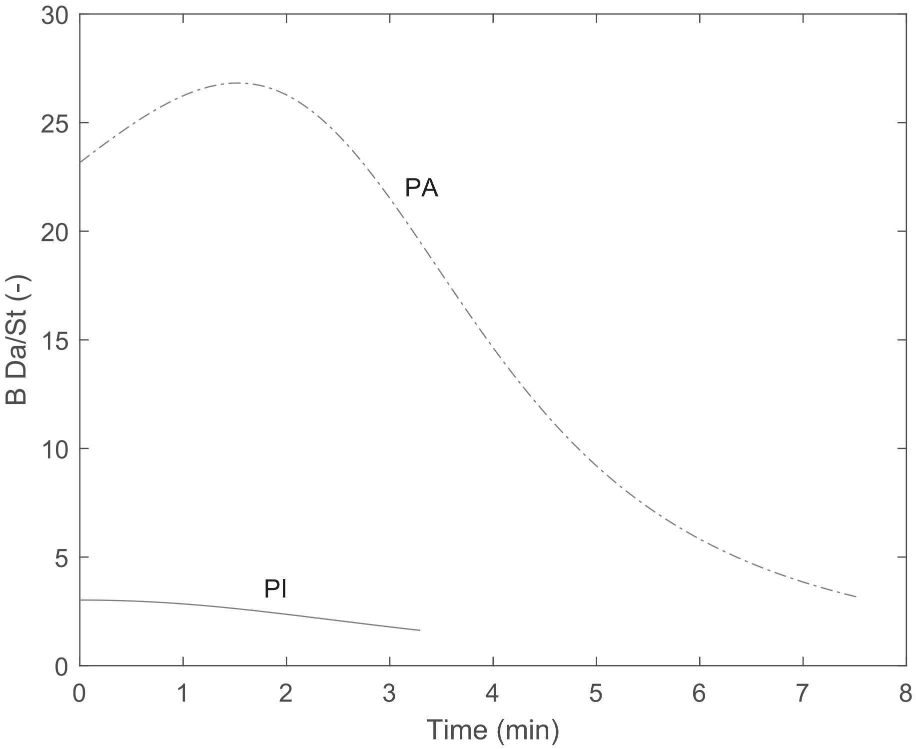


Fig. 5. Nitration of FAM to NIM in a 5 m^3 batch reactor equipped with a 12 m^2 cooling jacket (PA-labelled curve), extended through a 20 m^2 external plate-type heat exchanger (PI-labelled curve). B Da/St vs. time.

To recover a pseudo-isothermal regime at the industrial scale in the acceptable temperature range, the reactor had to be equipped with an external heat exchanger [24,31], which size could not be estimated through conventional tools in the absence of a kinetic characterization of the system.

According to the recommended temperature range, an average pseudo-isothermal temperature$\overline{T}_{PI} = 57.5\ ^\circ C$ could be calculated (step 1b of the flow chart of Fig. 2) which, with a minimum coolant loop temperature equal to $T_{cool} = 30\ ^\circ C$, led to a required St/Da ratio, calculated through equation (8), of about 1.5 (step 3a of the flow chart of Fig. 2).

To estimate the B value at the average pseudo-isothermal conditions, a suitable E_{app}/R value had to be estimated (step 1a of the flow chart of Fig. 2). In the literature an E_{app} /R value close to 10000 K for the solution polymerization of the current acrylic monomer can be found [37]. However, the presence of a water soluble crosslinker leads in this case to a rapid viscosity increase of the dispersed reaction phase, hence reducing the mobility of the living polymer chains and increasing the diffusion resistances of the reactants through the reaction mass itself. The resulting fast reaction regime makes in this case a halved E_{app} /R value (that is, 5000 K) more realistic. A corresponding B value equal to about 1.7 could be estimated (step 3b of the flow chart of Fig. 2). Therefore, $St/Da|_{PI} = \max\left(1.5; \frac{2}{3}1.7\right) = 1.5$ has been assumed (step 3c of the flow chart of Fig. 2).

From the measured temperature data, the corresponding Ψ and St/Da values under pseudo-adiabatic conditions can be estimated through equations (3) and (5), in the time range from the reaction onset to the peak temperature conditions (steps 3d and 3e of the flow chart of Fig. 2). At the time at which the maximum dT/dt was detected, a value of the ratio $(UA)_{ext}/(UA)_{jkt}$ ratio equal to of about 6 could be estimated (step 3f of the flow chart of Fig. 2), corresponding to an about 30 m^2 plate-type external heat exchanger (step 3 g of the flow chart of Fig. 2).

The stepwise results of the applied procedure are summarized in Table 2.

Note that sizing the additional heat transfer surface to be installed on the industrial reactor (having a 2 m internal diameter) through the simple adoption at the industrial scale of the same heat removal area per unit volume available on the laboratory equipment (having a 10 cm internal diameter) would have led to an unrealistic overestimation. In fact, being the heat transfer surface per unit volume roughly inversely proportional to its diameter, the surface provided by the lab-scale reactor would have been extended by a factor of 20, leading to a roughly 100 m^2 external plate-type heat exchanger.

In Fig. 7 the temperature and conversion trends sampled from the same industrial-scale reactor equipped with a 30 m^2 recycle loop plate-type exchanger are plotted, zoomed again in the region around the temperature peak: it can be noticed that the reactor behaviour is now pseudo-isothermal, with temperature peaks lower than 60 °C as required by the chemical recipe.

The comparison between the two reactor regimes (pseudo-adiabatic, PA, and pseudo-isothermal, PI) is shown in Fig. 8 in terms of B Da/St. Also in this case, the pseudo-isothermal conditions involve B Da/St values steadily close to the order of magnitude of 10^0, while the B Da/St values for the pseudo-adiabatic conditions sharply overcome the threshold order of magnitude of 10^1.

The additional heat transfer surface has been finally recalculated through the same procedure accounting for a ± 20 % change around the assumed E_{app}/R value. The resulting heat transfer surfaces still remain close to the installed value of 30 m^2.

4. Conclusions

The scale-up of exothermic intrinsically safe fine chemical processes in industrial batch reactors often occurs in a multipurpose logic without a kinetic characterization of the system because of time and resources constraints. However, because of the normal decrease of the heat transfer surface per unit reactor volume when scaling-up from the laboratory-scale to the industrial-scale the heat transfer surface provided by the industrial-scale reactor jacket is often insufficient. Even if

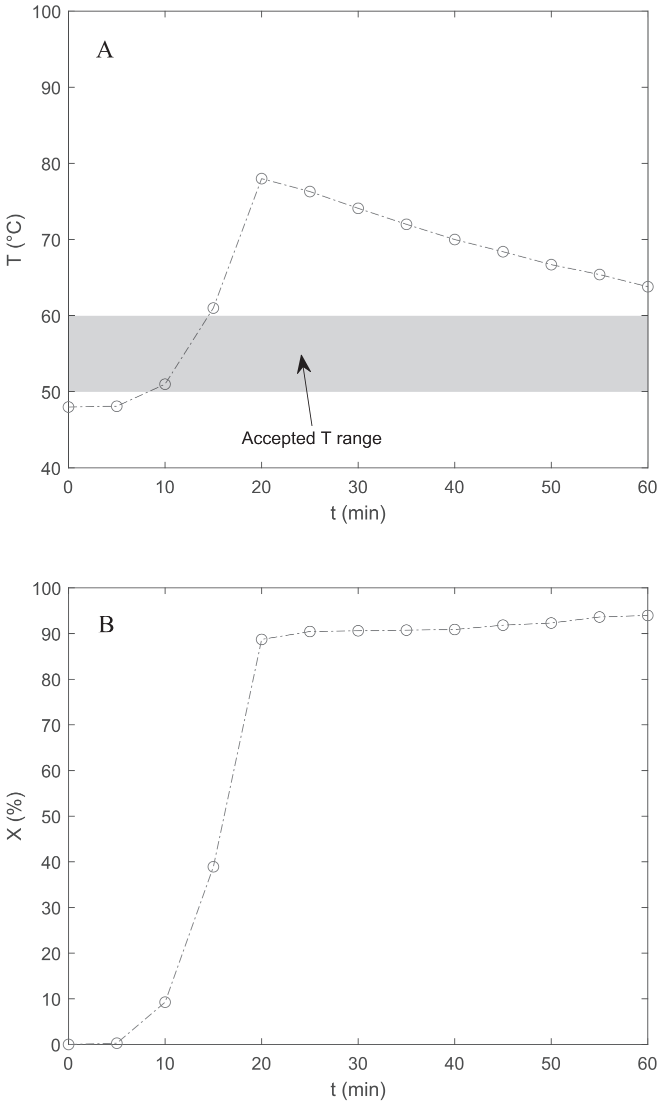


Fig. 6. Water-in-oil emulsion polymerization of an acrylic cationic monomer in a 15 m^3 batch reactor equipped with a 20.5 m^2 cooling jacket. (A) reactor temperature vs. time; (B) calorimetric conversion vs. time.

Table 2
Summary of the stepwise results for the acrylic emulsion polymerization.

Pseudo-isothermal regime characterization			
Recipe T range	55 ÷ 60 °C	$\overline{T}_{PI}$	57.5 °C
Recipe amounts	6807 kg MADQUAT MC75 9720 kg overall		
$\Delta\widetilde{H}_r$	−200 kJ/kg MADQUAT MC75	ΔT_{ad}	38 °C
$\widehat{C}_P$	3.68 kJ/(kg°C)	$St/Da\|_{eq.\ 8}$	1.45
$T_{cool,MIN}$	30 °C	2/3B	1.13
E_{app}/R	5000 K	$St/Da\|_{PI}$	1.45
Pseudo-adiabatic measurements			
T profile	See Fig. 6A		
U_{jkt}	0.30 kW/(m^2K)	T_{PA}	61 °C
U_{ext}	1.20 kW/(m^2K)	$St/Da\|_{PA}$	0.17
Additional heat transfer surface estimation			
		$(UA)_{ext}/(UA)_{jkt}$	6.55
A_{jkt}	20.5 m^2	A_{ext}	34 m^2 (plate-type)

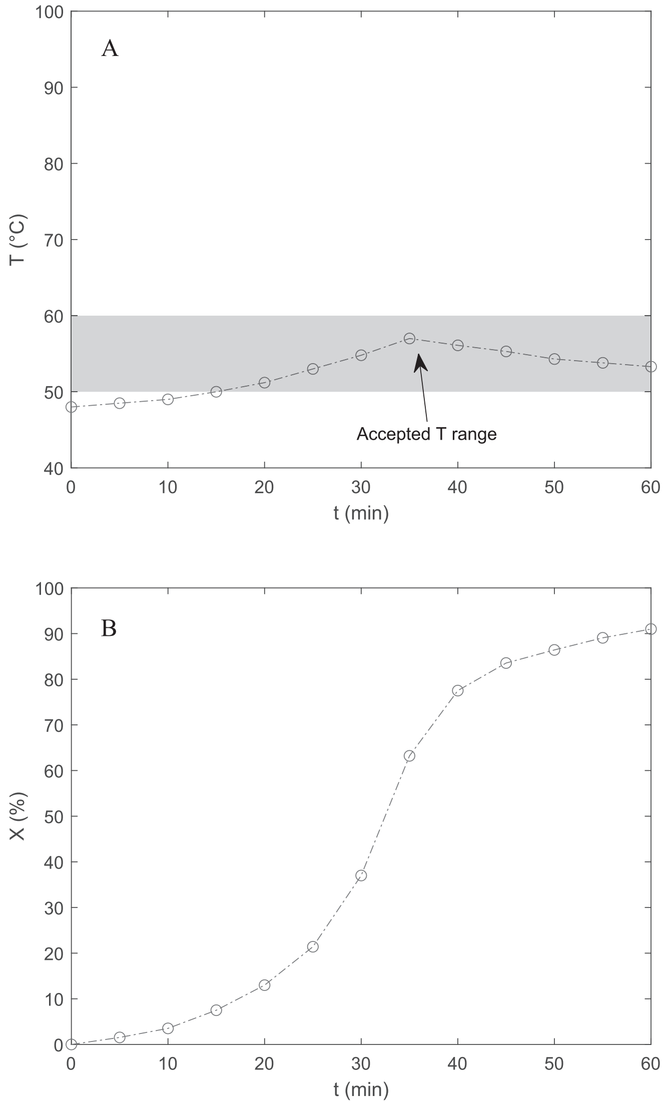


Fig. 7. Water-in-oil emulsion polymerization of an acrylic cationic monomer in a 15 m^3 batch reactor equipped with a 20.5 m^2 cooling jacket of and a 30 m^2 external plate-type heat exchanger. (A) reactor temperature vs. time; (B) calorimetric conversion vs. time.

dangerous reactor overpressures cannot build-up in the reactor, a loss of thermal control of the process can negatively affect the product quality. In these cases, the industrial-scale reactor must be equipped with an additional heat transfer surface.

In this work, a methodology has been presented allowing for an easy estimation of the required additional surface to be installed in an existing batch reactor on the basis of the pseudo-adiabatic temperature trends measured in the industrial-scale reactor before installing the external heat exchange loop, therefore not requiring a characterization of the chemical kinetics. The proposed methodology has been successfully validated through the analysis of some industrial data about two suitable reaction processes, that is the final nitration step for the synthesis of an API and a water-in-oil acrylic polymerization for the synthesis of a polycationic thickener used in the cosmetic industry.

CRediT authorship contribution statement

Francesco Maestri: Writing – original draft, Validation, Software, Methodology, Data curation, Conceptualization. **Federica Petrella:** Investigation, Formal analysis. **Renato Rota:** Writing – review &

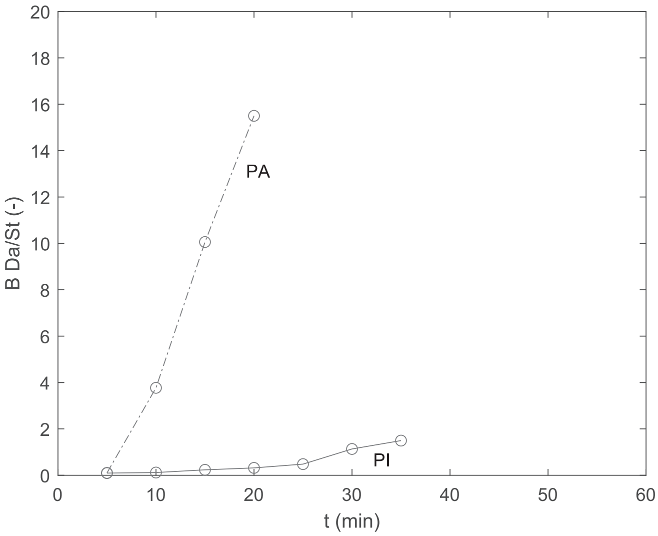


Fig. 8. Water-in-oil emulsion polymerization of an acrylic cationic monomer in a 15 m^3 batch reactor equipped with a 20.5 m^2 jacket (PA-labelled curve), extended through a 30 m^2 external plate-type heat exchanger (PI-labelled curve). B Da/St vs. time.

editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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