A simple procedure for optimal scale-up of fine chemical processes. Part I: practical tools.

Journal:	Industrial & Engineering Chemistry Research
Manuscript ID:	ie-2008-00465d.R2
Manuscript Type:	Article
Date Submitted by the Author:	17-Nov-2008
Complete List of Authors:	Rota, Renato; Dip. di Chimica Materiali e Ingegneria Chimica, Politecnico di Milano Maestri, Francesco; Politecnico di Milan, Gigante, Lucia; Stazione Sperimentale per i Combustibili, Lunghi, Angelo; Stazione Sperimentale per i Combustibili, Cardillo, Paolo; Stazione Sperimentale per i Combustibili, Copelli, Sabrina; Politecnico di Milano, Chimica, materiali e Ingegneria Chimica

SCHOLARONE[™] Manuscripts

A simple procedure for optimally scaling-up fine chemical processes.

Part I: practical tools.

Francesco Maestri, Sabrina Copelli, Renato Rota*

Politecnico di Milano Dip. di Chimica, Materiali e Ingegneria Chimica "G. Natta" via Mancinelli 7 - 20131 Milano - Italy fax: +39 0223993180; e-mail: <u>renato.rota@polimi.it</u>

Lucia Gigante, Angelo Lunghi, Paolo Cardillo

Stazione Sperimentale per i Combustibili viale De Gasperi 3 - 20097 San Donato Milanese - Milano - Italy

Abstract

A simple and general scale-up procedure, based on boundary and temperature diagrams safety criterion for exothermic semibatch reactors (SBRs), has been developed. Such a procedure is based on a few graphical correlations which allow end users, dealing with homogeneous as well as heterogeneous SBRs (with or without autocatalytic behavior), for an easy selection of safe operating conditions at the laboratory scale and for their scale-up to the industrial one, maximizing at the same time the industrial reactor productivity.

Keywords: Semibatch reactors; Scale-up; Safety; Productivity; QFS conditions; Temperature Rise

Curve.

^{*} to whom correspondence should be addressed

1. Introduction

In fine chemical and pharmaceutical industries, relatively fast and exothermic reactions are usually performed by adding, at a sufficiently low rate, one of the reactants (called coreactant) to the others, namely, using indirectly cooled semibatch reactors (SBRs).

Operating conditions of an exothermic SBR can be considered safe if they correspond to a sufficiently low coreactant accumulation so that cooling system can control the heat evolved by chemical reaction, hence limiting also reaction temperature rise. Once a set of safe operating conditions has been selected at laboratory scale, it must be scaled-up maximizing industrial reactor productivity.

The thermal loss of control of exothermic batch and semibatch reactors has been thoroughly analyzed in the literature. However, for a practical solution of the problem, any safety criterion and scale-up procedure must be simple and general at the same time. Such goals are often not easy to fit together, taking into account that, especially in fine chemical and pharmaceutical industries, a wide range of products, in relative small amounts, are produced and that a detailed mathematical model of every single process is often not affordable.

Methods presented in the literature for the selection of safe operating conditions of exothermic SBRs are all intended to minimize coreactant accumulation into the system.

Among the others, Hugo et. al.¹⁻³ firstly developed a semi-empirical criterion for homogeneous SBRs, which has been then extended to heterogeneous (liquid-liquid) reactors by Steensma and Westerterp⁴⁻⁶ and Westerterp and Molga⁷⁻⁹. These authors, on the basis of thermal effects associated to coreactant accumulation, provided a quantitative definition of accumulation phenomena in a SBR. In particular actual reactor temperature - time profile can be compared with a target one, corresponding to both a sufficiently low coreactant accumulation and to a very high reactor cooling efficiency. On the basis of such a comparison, the thermal behavior of the reactor itself can be classified. This information has been then represented in a suitable dimensionless space through the

so-called Boundary Diagrams (BDs), allowing end users to easily discriminate between safe and excessive accumulation operating conditions without solving the mathematical model of the reactor. This safety criterion has been experimentally validated by van Woezik and Westerterp^{10,11}, who studied the nitric acid oxidation of 2-octanol to 2-octanone with further oxidation of reaction product to unwanted carboxylic acids.

Maestri and Rota¹²⁻¹⁴ analyzed the role that estimated kinetic parameters play on conclusions drawn through boundary diagrams calculated for different reaction orders, proving that unjustified assumptions on the reaction kinetics cannot be accepted for a reliable application of the method: such a conclusion has been found to be true for both heterogeneous and homogeneous reaction systems and it makes a kinetic investigation (usually performed through calorimetric techniques) of great importance.

Moreover, a number of reacting systems are characterized by a threshold temperature value (in the following referred to as Maximum Allowable Temperature, MAT, which can arise either from chemical or safety constraints¹⁴), which must not be exceeded neither during normal nor during upset reactor operations. Therefore, limiting accumulation phenomena can be just a necessary, not a sufficient condition for the selection of a proper set of operating conditions for an exothermic SBR. For these reasons, Maestri and Rota^{14,15} introduced a new typology of diagrams, called Temperature Diagrams (TDs), to be coupled with boundary diagrams, allowing end users for a safe prediction of the maximum temperature increase with respect to initial reactor temperature. Combined boundary and temperature diagrams criterion has been previously validated by analyzing the industrial nitration process of N-(2-phenoxyphenyl) methane sulphonamide to N-(4-nitro, 2-phenoxyphenyl) methane sulphonamide¹⁶.

Molga et al.¹⁷ calculated BDs for homogeneous SBRs and (1,1) reaction order kinetics, providing diagrams for quick identification of inherently safe operating conditions. Maestri and Rota¹⁸ developed a safety criterion based on boundary and temperature diagrams for homogeneous SBRs with autocatalytic behaviour, for which the corresponding criterion developed for non-autocatalytic

reaction systems cannot be applied^{7-9,17}. Such a criterion involves initial catalyst amount as an additional parameter with respect to the non-autocatalytic case.

Once a set of safe operating conditions has been selected at the laboratory scale (e.g., through the usage of boundary and temperature diagrams) and validated through reaction calorimetry experiments (e.g., using a RC1 equipment), it must be scaled-up to the industrial reactor scale. However, such a scale-up process should be performed not only under safe conditions but also maximizing industrial reactor productivity. In the literature the problem of scaling-up safe operating conditions from laboratory to pilot and finally to full scale plant has been already analyzed on the basis of parametric sensitivity concepts: Alòs et al.¹⁹ applied the generalized parametric sensitivity criterion developed by Morbidelli et al.²⁰ to exothermic SBRs and analyzed the scale-up of an acid catalysed esterification process for the production of sec-butyl propionate. Recently Zaldivar et al.²¹⁻²⁴ developed an early warning criterion of runaway events, which can be applied to stirred tank reactors and for several kinetic schemes.

The method of boundary and temperature diagrams, as described in the literature, does not provide a procedure for optimally scaling-up a set of operating conditions verified at laboratory scale to full plant scale. Therefore, in this work, a simple procedure has been developed which, under Quick onset, Fair conversion, Smooth temperature profile (in the following referred to as QFS) operating conditions⁴ and through a generalized form of temperature diagrams, allows end users to scale-up safe operating conditions selected and verified at laboratory scale achieving, at the same time, safe and productive conditions.

2. Mathematical model

Since the mathematical model on which boundary and temperature diagrams method is based has been thoroughly discussed in the literature⁴⁻¹⁸, in the following it will be just briefly summarized. A single exothermic reaction of the form:

$$v_A A + v_B B \to C + v_D D \tag{1}$$

is assumed to occur. It is characterized by the following microkinetic rate expression:

$$r = k_{n,m} C_A^n C_B^m \tag{2}$$

The reaction system can be either homogenous (consisting of a single liquid phase) or heterogeneous (consisting of two liquid phases) and, in the latter case, reaction can occur either in the continuous or in the dispersed phase.

The following model assumptions can be reasonably stated:

- 1) the reaction mass is perfectly macromixed;
- 2) the influence of the chemical reaction on the volume of the single phase is negligible;
- 3) no phase inversions occur;
- 4) in the heterogeneous cases, the solubility of the species A (dosed coreactant) and C in the continuous phase, "c", and of components B (reactant initially charged into the reactor) and D in the dispersed phase, "d", is small;
- 5) in the heterogeneous cases, chemical reaction takes place only in one of the two liquid phases: this situation is very common in many industrial processes (such as nitrations and oxidations), in which the catalyst (typically a strong acid) is present only in one phase;
- 6) heat effects are associated to the chemical reaction only;
- reactor operates under isoperibolic conditions; in particular, at time equal to zero, reaction mass temperature is equal to mean coolant temperature and to dosing stream temperature (constant for the whole duration of the process).

Page 6 of 36

Mass balance equation for component B, at the beginning of the dosing period, can be written in dimensionless form as:

$$\frac{d\zeta_B}{d\theta} = v_A \, Da \, RE \, f \, \kappa_{n,m} \tag{3}$$

for homogeneous and heterogeneous (liquid-liquid) kinetically controlled reaction systems^{12,14} and in the form:

$$\frac{d\zeta_B}{d\vartheta} = v_A \, Da \, RE \, f \, \kappa_{n,m}^{1/2} \tag{4}$$

for heterogeneous (liquid-liquid) diffusion controlled reaction systems¹³. In equations (3) and (4) $Da=k_{n,m,R}t_DC_{B,0}^{n+m-1}$ is the Damköhler number for (n,m) order kinetics, which contains information about dosing time, and $\kappa_{n,m}=\exp[\gamma(1-1/\tau)]$ is the dimensionless reaction rate constant, which is the ratio of reaction rate constant to the same quantity evaluated at a reference temperature, T_R . $\gamma=E/(RT_R)$ is the dimensionless activation energy and $\tau=T/T_R$ is the dimensionless temperature.

Expressions for the calculation of reactivity enhancement factor, RE, and for function, f, have been derived elsewhere¹²⁻¹⁴ and they are summarized in Table 1.

Conversion rate, $d\zeta B/d\vartheta$, can be determined either by chemical reaction, mass transfer phenomena (in heterogeneous reaction systems) or coreactant supply.

Energy balance equation for the reactor can be rearranged as⁴:

$$\left(1 + \alpha R_H \varepsilon \vartheta\right) \frac{d\tau}{d\vartheta} = \Delta \tau_{ad,0} \frac{d\zeta_B}{d\vartheta} - \varepsilon \left[Co \left(1 + \varepsilon \vartheta\right) + R_H \right] \left(\tau - \tau_{cool}^{eff}\right)$$
(5)

where $Co = (UA)_0 t_D / (\tilde{\rho}_c \tilde{C}_{P,c} V_{r,0} \varepsilon)$ is cooling number, whose value is determined by heat transfer

efficiency of the reactor and dosing rate; $\tau_{cool}^{eff} = \frac{Co(1+\varepsilon \vartheta)\tau_{cool} + R_H\tau_D}{Co(1+\varepsilon \vartheta) + R_H}$ is an effective cooling

temperature which summarizes the enthalpic contributions of both coolant and dosing stream heat removal; α is a flag parameter which is equal to $1/R_{\rm H}$ or 1 for homogeneous or heterogeneous (liquid-liquid) reaction systems, respectively.

Equations (3) to (5), which have been derived for $0 < 9 \le 1$, can be easily extended to 9 > 1 by ACS Paragon Plus Environment substituting everywhere $(\vartheta - \zeta_B)/\vartheta$ or $(\vartheta - \zeta_B)$ terms with $(1 - \zeta_B)$, $\varepsilon \vartheta$ terms with ε and setting $T_D \equiv T$ in the definition of the effective cooling temperature.

3. <u>Safety criterion</u>

When dealing with relatively fast and exothermic reactions, a safe process operation can be achieved performing the reaction itself in an indirectly cooled SBR in which coreactant accumulation is kept at sufficiently low values so that the available cooling system can balance the enthaplic contribution due to the conversion rate.

On this basis, boundary and temperature diagrams method allows for a quick selection of reactor operating conditions implying both a sufficiently low coreactant accumulation and a reaction temperature increase, under isoperibolic conditions, lower than the Maximum Allowable Temperature ¹⁵. As mentioned elsewhere in the literature¹⁵, MAT is not a thermodynamic parameter of the system but it is only related to safety (when dangerous decomposition reactions can be triggered) or productivity problems (when undesired side reactions can lower process selectivity or influence product quality) which may affect the analyzed process. In both cases, MAT value corresponds to a reaction mass temperature at which a suitable calorimetric equipment (such as ARC or PHI-TEC II) is able to detect the onset of an exothermic phenomenon (e.g, a self heating rate of reaction mass larger than 0.02 °C/min) during a standard Heat-Wait-Search (HWS) test.

Once, for a given reaction system, microkinetic parameters have been experimentally estimated (e.g., through adiabatic ARC or Phi-TEC II experiments), the SBR thermal behavior (according to the model presented in the previous section) can be represented in a suitable dimensionless space of two parameters, called exothermicity, E_x , and reactivity, R_y , number, the former depending on reaction enthalpy and the latter accounting for initial dependence of the reaction rate on temperature:

$$E_{x} = \frac{\gamma}{\tau_{cool}^{2}} \frac{\Delta \tau_{ad,0}}{\varepsilon \left(Co + R_{H}\right)} \tag{6}$$

$$R_{y} = \frac{v_{A} Da RE \kappa|_{\tau_{cool}}}{\varepsilon (Co + R_{H})}$$
(7)

In these relations an apparent activation energy (which, for heterogeneous diffusion controlled systems, is equal to half of the corresponding microkinetic value) has to be used.

In this dimensionless space a boundary can be calculated⁴ (see Figure 1), inside which an excessive coreactant accumulation occurs. This means that, in this region, a target temperature defined as⁴:

$$\tau_{ta} = \tau_{cool}^{eff} + 1.05 \frac{\Delta \tau_{ad,0}}{\varepsilon \left[Co \left(1 + \varepsilon \vartheta \right) + R_H \right]}$$
(8)

is exceeded. The target temperature relation can be extended to 9>1 by substituting the $\epsilon 9$ term with ϵ .

The aforementioned excessive accumulation region is included in a larger domain, bounded by $R_y=R_{y,QFS}$ and $E_x=E_{x,MIN}$ lines, which identifies inherently safe operating conditions.

In particular, QFS line shows a maximum because a reduction in E_x leads at first to a delayed temperature rise during dosing time, thus requiring higher R_y values to avoid dangerous accumulation. However, further reducing E_x , thermal effects of coreactant accumulation are so small to imply a lowering in R_y value.

At $E_x \le E_{x,MIN}$ accumulation of unreacted coreactant in the reaction system during dosing period still increases at lower R_y values, but thermal effects associated to it (quantified through the exceeding of the target temperature) are always negligible because of too low reaction exothemicity. On this basis, a simplified safety criterion can be stated, according to which only operating conditions characterized by a sufficiently low unreacted coreactant accumulation are accepted, independently on reaction exothermicity. Such a safety criterion can be summarized for any E_x value through the following condition:

$$R_{y} \ge R_{y,QFS} \tag{9}$$

In the literature^{1-3,9} a number of safety criteria of this type can be found: as an example, the criterion of Hugo and Steinbach¹ for homogeneous SBRs with (1,1) reaction orders, states that only

operating conditions characterized by R_y values higher than one can be accepted, which complies with $R_{y,QFS}$ value calculated through boundary diagrams¹⁴.

Moreover, selecting even at $E_x \le E_{x,MIN}$, operating conditions characterized by $Ry \ge R_{y,QFS}$ improves reactor productivity: moving from operating conditions A to B in Figure 1, through an initial reaction temperature increase (if allowed according to MAT constraint), the conversion at the end of the supply period is higher and the further batch period after the end of coreactant dosing (in which the reaction reaches full conversion) can be shortened.

 $R_{y,QFS}$ values for the whole set of cooling numbers of industrial relevance are represented in Figures 2 and 3. Such curves, in the following referred to as Inherently Safe Conditions curves (ISC), provide safe $R_{y,QFS}$ values dependent on reaction order with respect to coreactant, n, but independent on the estimated reaction order with respect to reactant initially charged into the reactor, m, (because of low parametric sensitivity of $R_{y,QFS}$ with respect to m). Limiting the variation range of n between 0.5 and 2, only ISC curves for n=1 and n=2 (n=0.5) have been reported since for homogeneous (heterogeneous) systems $R_{y,QFS}$ value increases (decreases) with n.

Note that a low Co value can be related either to a short dosing time or to a low heat transfer rate which, at the beginning of the dosing period, can cause a temperature rise delay and, consequently, some coreactant accumulation. As a results, $R_{v,OFS}$ vs. Co curves can exhibit a maximum.

Figures 2 and 3 allow end users for a safe and easy selection of low accumulation operating conditions. It is worth mentioning that, in our knowledge for heterogeneous reaction systems, no $R_{y,QFS}$ values had been ever published in the literature for the lowest cooling number values (which are most frequently encountered at the industrial scale) and for reaction orders with respect to the dosed coreactant, n, lower than one, for which n=1 values can not be safely employed^{12,13}. Moreover, from Figures 2 and 3, it can be observed that, independently on reaction system, the average sensitivity of $R_{y,QFS}$ with respect to Co for n=1 cases represented is usually lower than that for n≠1 cases (for which $R_{y,QFS}$ values calculated assuming n=1 can not be safely employed). Also for this reason in such cases the availability of $R_{y,QFS}$ data extended to the whole set of Co values of

industrial relevance is of crucial importance. ISC curves reported in Figures 2 and 3 have been calculated at R_H =1 except for homogeneous reaction case, for which the sensitivity of $R_{y,QFS}$ with respect to R_H is negligible¹⁴. In heterogeneous cases it must be taken into account that a lower R_H value (such that occurring when an organic phase is added to an aqueous one⁷) leads to a higher $R_{y,QFS}$ value at the current Co, since enthalpic contribution of dosing stream (and hence its cooling capability) is lower. Such an $R_{y,QFS}$ increase is significant just for n≠1 cases, for which a 15% higher value with respect to that corresponding to R_H =1 case can be safely assumed^{12,13}.

Under QFS conditions the characteristic time of the process (which is related to the overall conversion rate as well as to its enthalpic effects) is, at the same time, close to dosing time and much higher than the characteristic time of reaction mass cooling. This means that system thermal behavior is fully determined by the enthalpic contribution of the reaction and the kinetic parameters (that is: n and m) as well as the heat transfer parameters (that is: Co and R_H) have a small influence on the system thermal behavior. Under such conditions, as demonstrated for autocatalytic reaction systems¹⁸, the dimensionless maximum temperature rise (that is, $\Psi = (T_{max}/T_0)_{max}$) in the representation of temperature diagrams¹⁴, (which is in general a function of Co, R_H, n, m, R_y and E_x) becomes, as a first approximation, a function of E_x only and, consequently, all ψ vs. E_x curves (for homogeneous as well as heterogeneous reaction systems with a slow or fast reaction occurring in the dispersed or in the continuous phase) tend to overlap into a narrow region, as can be seen from raw data represented in Figure 4, whose superior boundary defines a general curve called Temperature Rise Curve (TRC). In particular, points appearing in Figure 4 represent calculated ψ values in a wide range of Co, R_H, n and m parameters, and at R_y values such that R_y≥R_{x,QFS}.

It should be noticed that in the representation of TRC curve the same definition of the exothermicity and reactivity numbers (that is, the one based on the microkinetic value of the activation energy) has been used, also for heterogeneous diffusion controlled systems for which the apparent activation energy is equal to the half of its microkinetic value. In fact, once QFS operating conditions are Page 11 of 36

attained, the behavior of heterogeneous reaction systems can not be determined by mass transfer phenomena, since dosing time is much higher than all the other characteristic times. Moreover, since under QFS conditions the role of reaction kinetics becomes less important, the same temperature rise curve can be used for estimating maximum peak temperature also of autocatalytic reaction systems, as can be observed from Figure 4, where also ψ data for homogeneous autocatalytic systems have been superimposed. In this case, $R_{y,QFS}$ values for the selection of low accumulation operating conditions as well as full details on diagrams can be found elsewhere¹⁸. TRC curve can therefore be used for a safe and general estimation of the maximum peak temperature for any of the aforementioned systems and any combination of Co, R_H , n, m (and $\zeta_{B,0}$) parameters into their specified range of variation, checking then that operating conditions selected are characterized by an R_y value higher than the corresponding $R_{y,QFS}$.

It must be finally noticed that the usage of TRC diagram (and hence the criterion in question) is based on QFS conditions. A low parametric sensitivity of the reactor's behavior with respect to the different process and plant parameters can therefore be expected, as a difference with excessive accumulation operating conditions. Such a characteristic is very important in order to smooth the effect of eventual inaccuracies in the estimation of the parameters involved.

4. <u>Scale-up procedure</u>

TRC and ISC diagrams, through which it is possible to easily select at laboratory scale (that is, at RC1 scale) safe and productive operating conditions for an exothermic SBR, can also be used to perform a safe scale-up to industrial scale. The five-steps procedure to do this is described in the following and finally represented in the flow chart of Figure 5:

1) Execution of calorimetric screening tests in order to characterize thermal behavior of reactants, products and reacting mixture in a suitable temperatures range. In particular DSC (Differential Scanning Calorimetry) experiments must be performed on reactants and products to detect if they may be affected by thermal decomposition or oxidation in the selected range of investigated

temperatures (e.g., in tests using inox sample holders temperatures vary between 40 and 280 °C). Then it must be carried out a standard Heat-Wait-Search (HWS) test on the reacting mixture by using an ARC (Accelerated Rate Calorimeter) equipment: such an experiment provides MAT parameter as it has been previously defined (e.g self heating rate of reaction mass larger than 0.02 °C/min).

2) Execution of adiabatic tests (in an RC1 or PHI-TEC II equipment) in order to obtain microkinetic rate expression (power law form). When treating with heterogeneous systems, such experiments must be performed at different agitator speed to identify operating conditions where temperature profiles stop to be affected by mass transfer phenomena, that is we are in kinetically controlled (or slow) reaction regime.

3) Knowing process recipe and a suitable initial reactor temperature T_0 , it is possible to use TRC and ISC diagrams in order to identify safe and productive operating conditions at laboratory scale (namely, at the RC1 scale). The strategy is based on the main process variables of the system which are initial reaction temperature, T_0 , and dosing time, t_D . Since initial reaction temperature arises mainly from chemical recipe, according to safety and product quality constraints, the procedure in question will be based on dosing time, t_D , as the only process parameter.

On TRC diagram, from a ψ value corresponding to an Effective Maximum Allowable Temperature (EMAT), ψ_{EMAT} , lower than the MAT value obtained by the ARC test, obtained through a parameter *toll* (EMAT = MAT(1-*toll*); this is a conservative assumption which allows us to prevent dangerous effects if there is a certain degree of uncertainty in MAT estimation), it is possible to read off the corresponding E_x value, $E_{x,EMAX}$, which is the maximum acceptable value of exothermicity number at laboratory scale. Since all the other dimensionless parameters appearing in the E_x expression (6) but Co are known, to a maximum E_x value a minimum value of the cooling number corresponds ($Co_{MIN} = \gamma \Delta \tau_{ad,0} / \tau_0^2 \varepsilon E_{x,MAX} - R_H$) and finally (being physical and heat transfer characteristics of RC1 known) also a minimum dosing time

 $(t_{D,MIN,RC1} = Co_{MIN} \tilde{\rho}_c \tilde{C}_{P,c} V_c \varepsilon / (UA)_0$). From calculated $t_{D,MIN,RC1}$ value it is possible to evaluate system reactivity number, $R_{y,RC1}$, and check, using a suitable ISC diagram, if such a reactivity number is major of the correspondent $R_{y,QFS}$ value (evaluated at the Co_{MIN} value previously determined). If $R_{y,RC1} > R_{y,QFS}$ the calculated operating conditions are accepted; if $R_{y,RC1} < R_{y,QFS}$ a lower ψ_{EMAT} value must be assumed and all steps described in point 3) repeated. It should be noticed that even operating conditions which satisfy the check $\psi T_0 \leq EMAT$ cannot be considered thermally safe if they imply an excessive coreactant accumulation: in fact they must be safe not only during the normal reactor operation, but also during upset conditions (such as those arising from a cooling system failure). In such situations, operating with a minimum coreactant accumulation allows to keep the process safe by stopping immediately the coreactant feed.

4) Selected operating parameters (T_0 and $t_{D,MIN,RC1}$) must be then experimentally validated through, at least, one RC1 experiment.

5) Once a suitable set of safe operating conditions has been selected and verified at the laboratory (RC1) scale, it must be scaled up to the industrial plant. In a scale-up process it is crucial that any variation of process variables is inherently safe. When moving from laboratory to the full plant scale, dosing time increases. However, in order to maximize reactor productivity, we are interested in limiting as much as possible such dosing time increase, while keeping safe conditions. Such a problem can be easily solved by repeating the same procedure used at RC1 scale in order to obtain minimum laboratory dosing time. Through the general temperature rise curve of Figure 4, from a ψ value corresponding to the Effective Maximum Allowable Temperature (EMAT), ψ_{EMAT} , even used at RC1 scale, it is possible to read off the corresponding maximum value of exothermicity number acceptable at industrial scale, $E_{x,\text{EMAX}}$. It should be noted that $E_{x,\text{EMAX}}$ calculated from TRC diagram is independent on scale considered because only dimensionless parameters are involved in its definition. As we have previously said, to a maximum E_x value a minimum value of cooling number corresponds ($Co_{MIN} = \gamma \Delta \tau_{ad,0}/\tau_0^2 \varepsilon E_{x,MAX} - R_H$) and therefore (being physical and heat transfer

characteristics of industrial reactor known) also a minimum industrial dosing time $(t_{D,MIN,ind} = Co_{MIN} \tilde{\rho}_c \tilde{C}_{P,c} V_c \varepsilon / (UA)_0)$. From calculated $t_{D,MIN,ind}$ value it is possible to evaluate industrial reactivity number, $R_{y,ind}$, and check, using a suitable ISC diagram, if such a reactivity is larger than the correspondent $R_{y,QFS}$ value (evaluated at the Co_{MIN} value previously determined). For what concerns the estimation of the maximum E_x value, at laboratory or industrial scale, with respect to the MAT constraint, it could be observed that under QFS conditions the peak reaction temperature as well as the local value of the target temperature (8) is always lower than its initial value, $T_{ta,0}$. Therefore, the functional dependence of the initial target temperature, $T_{ta,0}$, on the exothermicity number (arising from a simple combination of equations (6) and (8)) could be also assumed as a safe estimation of the peak reaction temperature itself and hence used for estimating the corresponding maximum E_x value with respect to the MAT constraint. Such a functional dependence yields:

$$\frac{\tau_{ta,0}}{\tau_0} = 1 + 1.05 \frac{\tau_0}{\gamma} E_x \tag{11}$$

According to the range of variation of γ parameter assumed in the calculation of TRC and ISC diagrams and taking into account that initial temperature values fall reasonably in the range -20 $\div 100^{\circ}$ C (corresponding to $\tau_0=0.85\div1.25$, with T_R=300K), quantity (11) varies between 1+0.02E_x and 1+0.04E_x, as represented through the two straight lines plotted in Figure 4 (note that the legend "industrial operating region" in Figure 4 refers to the slope range of target temperature lines corresponding to the aforementioned industrial operating conditions).

As discussed elsewhere for autocatalytic reaction systems¹⁸, it can be noticed that, at low E_x values $(E_x < 5)$, initial target temperature can be a satisfactorily approximation of the maximum peak temperature as estimated through TRC diagram of Figure 4. However, at high E_x values (corresponding either to low Co values or high $\Delta \tau_{ad,0}$ values), ψ vs. E_x behavior deviates from linearity (see equation (10)) and the usage of initial target temperature (8) to estimate maximum peak temperature becomes less accurate and can lead to huge overestimations with respect to the

ACS Paragon Plus Environment

value estimated through temperature rise curve. In fact, at low Co values (corresponding to high E_x values) the ratio of the characteristic time of the process (which is close to dosing time) with respect to that one characteristic of reaction mass cooling (which, under QFS conditions, is equal to $\epsilon(Co+R_H)$) can be not sufficiently high¹⁸. Since conditions characterized by low Co values are normally encountered at industrial scale⁷⁻⁹, it can be concluded that the usage of $T_{ta,0}$ value for estimating peak reaction temperature with respect to MAT constraint and the corresponding maximum E_x value would lead to the selection of scaled-up operating conditions which can lower industrial reactor productivity.

However, under different operating conditions, the value of initial target temperature (which can be never overcome by real peak reaction temperature) can be a better estimation of the peak temperature than the value provided by general temperature rise curve, as always shown by Figure 4, where a region characterized by values of initial target temperature lower than that provided by temperature diagrams can also exist.

This leads to a simple rule of thumb for selecting maximum E_x value at industrial scale for optimizing reactor productivity: once both E_x values corresponding to EMAT (through equation (11) and through the general temperature rise curve of Figure 4, equation (10)) have been calculated, the higher of these two values must be assumed to evaluate scaled-up cooling number and the corresponding dosing time.

Finally, scaled-up operating conditions must be checked for coreactant accumulation problems using proper $R_{y,QFS}$ vs. Co curve. Moving from laboratory to industrial operating conditions, R_y value increases since dosing time increases inevitably. Therefore, even in cases in which $R_{y,QFS}$ is a decreasing function of Co, R_y value at industrial scale is unlikely to be lower than $R_{y,QFS}$ value corresponding to the current industrial Co value. Consequently, if scaled-up conditions are characterized by an R_y value still higher than $R_{y,QFS}$ value corresponding to industrial cooling number, they can be accepted. Otherwise, a lower ψ_{EMAT} must be selected at industrial scale, in order to fulfill the $R_y > R_{y,QFS}$ constraint.

5. <u>Sensitivity analysis</u>

The combined optimization – scale-up procedure previously described uses a series of experimental parameters inevitably subjected to uncertainty. In order to define *how safe* a determined set of selected operating conditions can be, it is necessary to perform a sensitivity analysis with respect to all parameters subjected to uncertainty²⁵. The simplest way to execute such an analysis is to perform a numerical sensitivity analysis as discussed in the following procedure.

Let us consider a generic experimental parameter, β , subjected to a certain degree of uncertainty ε . Real β value, β_{real} , falls between a minimum and a maximum threshold value dependent on the calculated (from experimental measurements) parameter β_{calc} , as reported in (12):

$$\beta_{calc}(1-\varepsilon) \le \beta_{real} \le \beta_{calc}(1+\varepsilon) \tag{12}$$

 β_{cale} is the value used to perform the aforementioned TRC and ISC optimization - scale-up procedure. Once this procedure has been carried out, if check on ISC diagram is positive (no excessive coreactant accumulation is attained) a numerical sensitivity analysis should be carried out to ensure that the selected $t_{D,MIN}$ value leads to safe conditions even if the real value of some parameters differs from the calculated one. Consequently, using β values equal to both $\beta_{cale}(1-\epsilon)$ and $\beta_{cale}(1+\epsilon)$ while keeping unchanged $t_{D,MIN}$, TRC and ISC optimization – scale-up procedure has to be repeated. If the check on ISC diagram is positive for both cases we may conclude that no dangerous sensitivity of the procedure with respect to parameter β exists and that the selected operating conditions are inherently safe. If at least one of the two ISC checks is not passed it is necessary to repeat the optimization – scale-up procedure decreasing the previously selected Ψ_{EMAT} value until all ISC checks are positive. Such a new value of Ψ_{EMAT} permits to recalculate a maximum process exothermicity, $E_{x,EMAT}$, lower than the previous one and a minimum cooling number (and so a minimum dosing time) larger than that one previously computed. Consequently, R_y , which is proportional to the dosing time, will be higher.

This sensitivity analysis is not too cumbersome. However, for homogeneous and heterogeneous kinetically controlled systems, it is possible to obtain a few analytical relations to perform such an

analysis more rapidly. This results in some simple criteria which, using the calculated parameters value, β_{calc} , allow to predict when a computed $t_{D,MIN}$ leads to inherently safe conditions. Such relations, available in the form $R_{y,calc} > F_1 R_{y,QFS,calc}$ and $\varepsilon < F_2$, are summarized in Table 2 for heterogeneous kinetically controlled systems. Moreover, Table 3 provides analytical expressions for involved normalized sensitivity coefficients²⁵.

Such criteria can be easily determined by deriving, firstly, analytical relations for normalized sensitivity coefficients $S_{\beta/\alpha} = \alpha/\beta \cdot \frac{\partial \beta}{\partial \alpha}$ (being β a target parameter and α an operating parameter) and, secondly, by enforcing the following constraints:

$$R_{y,real} > R_{y,QFS,real} \tag{13}$$

$$\Psi_{real} < \Psi_{MAT} \tag{14}$$

where:

- $R_{y,real}$ is the real reactivity number value, related to the calculated (from TRC ISC procedure) one through the relative uncertainty, ε , and other calculated parameters of the system (Co_{MIN}, R_H, γ , τ_0 , C_{B,0}, m_A, ...);
- $R_{y,QFS,real}$ is the actual $R_{y,QFS}$ value, which is related to the calculated one by the relative uncertainty, ε , and the sensitivity coefficients $S_{R_{y,QFS}/Co}$ and $S_{R_{y,QFS}/n}$;
- Ψ_{real} is the real attainable dimensionless temperature increase with respect to initial reactor temperature, T₀, which is related to the calculated one (Ψ_{EMAT}) through the relative uncertainty ε and through the tolerance, *toll*, on the MAT parameter estimated by the ARC HWS test;
- Ψ_{MAT} is the ratio of maximum allowable temperature with respect to initial reactor temperature.

Therefore, starting from the relative degree of uncertainty of a given parameter, ε , and simply computing F₁ and F₂ groups, it is possible to verify whether the selected operating conditions are

safe or not, even when experimental parameters involved in the TRC and ISC optimization – scaleup procedure are subjected to uncertainty.

6. Conclusions

In this work a simple and general scale-up procedure for optimally scaling-up safe operating conditions verified at the laboratory scale for exothermic SBRs has been developed and presented. Such a scale-up procedure not only allows to keep safe conditions but also to maximize industrial reactor productivity.

Method developed, based on QFS operating conditions (ISC diagrams) and a generalized form of temperature diagrams (TRC diagram), allows end users (dealing with homogeneous as well heterogeneous slow or fast semibatch reactions, occurring in the dispersed or in the continuous phase and even homogeneous autocatalytic systems) for a safe and easy scale-up, which also maximizes industrial reactor productivity.

Once a set of operating conditions has been selected and experimentally validated at laboratory scale, TRC diagram (or initial target temperature) can be used in order to identify maximum exothermicity number at industrial (laboratory) scale with respect to the system EMAT constraint. To such a maximum value of E_x a minimum cooling number and hence a minimum dosing time at industrial scale corresponds. Then, the scaled-up conditions must be verified with respect to coreactant accumulation through the $R_{y,QFS}$ vs. Co curves (ISC diagrams). If industrial R_y is lower than the corresponding $R_{y,QFS}$ value, a lower EMAT value has to be assumed to which a higher minimum dosing time will correspond. Finally, a sensitivity analysis of the optimization – scale-up procedure with respect to all experimental parameters subjected to uncertainty should be performed in order to classify as inherently safe the selected operating conditions.

<u>Nomenclature</u>		
А	heat transfer area of the reactor (associated to the jacket and/or the coil), m^2	
А	preexponential factor, $m^{3(n+m-1)}/(kmol^{n+m-1}\cdot s)$	
С	molar concentration, kmol/m ³	
Со	= $\left(UA\right)_{0} t_{D} / \left(\tilde{\rho}_{c} \tilde{C}_{P,c} V_{c} \varepsilon\right)$, cooling number, -	
$ ilde{C}_P$	molar heat capacity, kJ/(kmol·K)	
d _{b,0}	d _b at hold up of the dispersed phase approaching zero, m	
D	diffusivity, m ² /s	
Da	$=k_{n,m,R}t_DC_{B,0}^{n+m-1}$, Damköhler number for (n,m) order reactions, -	
Е	activation energy, kJ/kmol	
$E_{\mathbf{x}}$	exothermicity number, eq. (6), -	
EMAT	=(1- <i>toll</i>) MAT, effective maximum allowable temperature, K	
F	function of the dimensionless time and conversion of B in eqs. (3) and (4) , -	
$F_{1/2}$	security factors in checks on optimization - scale-up procedure sensitivity, -	
$\Delta \tilde{H}$	reaction enthalpy, kJ/kmol	
$k_{n,m} \\$	reaction rate constant, $m^{3(n+m-1)}/(kmol^{n+m-1}\cdot s)$	
М	Equilibrium distribution coefficient ($m_A=C_{A,c}/C_{A,d}$; $m_B=C_{B,d}/C_{B,c}$), -	
MAT	maximum allowable temperature, K	
r	reaction rate referred to the total liquid volume, $kmol/(m^3 \cdot s)$	
R	gas constant = 8.314 , kJ/(kmol·K)	
RE	reactivity enhancement factor in eqs. (3) and (4), -	
$R_{\rm H}$	$=\widetilde{\rho}_{d}\cdot\widetilde{c}_{p,d}/\widetilde{\rho}_{c}\cdot\widetilde{c}_{p,c}$, heat capacity ratio, -	
R_y	reactivity number, eq. (7), -	
Т	time, s	
Т	temperature, K	

U	overall heat transfer coefficient, $kW/(m^2 \cdot K)$
---	---

Subscripts and superscripts

A,B,C,D	components A, B, C and D
Ad	Adiabatic
В	in the dispersed phase drop diameter d _b
С	continuous phase
Cool	Coolant
d	dispersed phase
D	dosing stream or dosing time
Eff	Effective
Fast	fast reaction regime
Н	in the heat capacity ratio R _H
IND	at the industrial scale
L	in the liquid phase
LAB	at the laboratory scale
Μ	order of reaction respect to component B
MAT	at the maximum allowable temperature
max or MAX	maximum value of a quantity or at the maximum value of a quantity
n	order of reaction respect to component A
MIN	in E _{x,MIN}
QFS	in R _{y,QFS}
R	Reference
Slow	slow reaction regime
toll	safety parameter for MAT value: $EMAT = (1-toll) MAT$

1		
2 3 4	Х	in the exothermicity number E_x
5 6	Y	in the reactivity number R _y
7 8 9	0	start of the semibatch period
10 11		
12 13 14	Greek sy	vmbols
15 16	α	flag parameter in eq. (5), -
17 18	γ	= $E/(RT_R)$, dimensionless activation energy, -
20 21	3	relative volume increase at the end of the semibatch period, -
22 23	3	relative error in sensitivity analysis
24 25 26	ζ	molar conversion, -
27 28	ζ	initial catalyst amount for autocatalytic reaction systems, -
29 30 31	θ	=t/t _D , dimensionless time, -
32 33	к	= k/k_R , dimensionless reaction rate constant, -
34 35 36	ν	stoichiometric coefficient, -
37 38	$ ilde{ ho}$	molar density, kmol/m ³
39 40 41	τ	= T/T_R , dimensionless temperature, -
42 43 44 45 46	$\Delta au_{ad,0}$	$= \frac{\left(-\Delta \tilde{H}_{r}\right)C_{B,0}}{v_{B}\tilde{\rho}_{c}\tilde{C}_{P,c}\cdot T_{R}}, \text{ dimensionless adiabatic temperature rise, -}$
47 48 49 50	Ψ	= $(T_{max}/T_0)_{max}$, maximum dimensionless temperature rise, -
51 52 53		
54 55 56		
57 58		
59		

Literature cited

- Hugo, P.; Steinbach, J. Praxisorientierte Darstellung der Thermischen Sicherheitsgrenzen f
 ür den Indirekt Gek
 ühlten Semibatch-reaktor. *Chem. Ing. Tech.* **1985**, *57*, 780.
- (2) Hugo, P.; Steinbach, J. A Comparison of the Limits of Safe Operation of a SBR and a CSTR. *Chem. Eng. Sci.* , *41*, 1081.
- (3) Hugo, P.; Steinbach, J.; Stoessel, F. Calculation of the Maximum Temperature in Stirred Tank Reactors in Case of a Breakdown of Cooling. *Chem. Eng. Sci.* **1988**, *43*, 2147.
- (4) Steensma, M.; Westerterp, K. R. Thermally Safe Operation of a Cooled Semi-batch Reactor. Slow Liquid-liquid Reactions. *Chem. Eng. Sci.* 1988, 43, 2125.
- (5) Steensma, M.; Westerterp, K. R. Thermally Safe Operation of a Semibatch Reactor for Liquid-Liquid Reactions. Slow Reactions. *Ind. Eng. Chem. Res.* 1990, 29, 1259.
- (6) Steensma, M.; Westerterp, K. R. Thermally Safe Operation of a Semibatch Reactor for Liquidliquid Reactions. Fast Reactions. *Chem. Eng. Technol.* 1991, 14, 367.
- (7) Westerterp, K.R.; Molga, E.J. No More Runaways in Fine Chemical Reactors. *Ind. Eng. Chem. Res.* 2004, 43, 4585.
- (8) Westerterp, K. R.; Molga, E. J. Runaway Prevention in Liquid-liquid Semibatch Reactors. *Inzynieria Chemiczna i Procesowa* 2004, 25, 2041.
- (9) Westerterp, K. R.; Molga, E. J. Safety and Runaway Prevention in Batch and Semibatch Reactors – A review. *Chem. Eng. Res. Des.* 2006, 84, 543.
- (10) van Woezik, B. A. A.; Westerterp K. R. The Nitric Acid Oxidation of 2-octanol. A Model Reaction for Multiple Heterogeneous Liquid-liquid Reactions. *Chem. Eng. Process.* 2000, 39, 521.
- (11) van Woezik, B. A. A.; Westerterp K. R. Runaway Behaviour and Thermally Safe Operation of Multiple Liquid-liquid Reactions in the Semibatch Reactor. The Nitric Acid Oxidation of 2octanol. *Chem. Eng. Process.* 2001, *41*, 59.

- (12) Maestri, F.; Rota, R. Thermally Safe Operation of Liquid-liquid Semibatch Reactors. Part I: Single Kinetically Controlled Reactions with Arbitrary Reaction Order. Chem. Eng. Sci.
 - 2005, 60, 3309. (13) Maestri, F.; Rota, R. Thermally Safe Operation of Liquid-liquid Semibatch Reactors. Part II: Single Diffusion Controlled Reactions with Arbitrary Reaction Order. Chem. Eng. Sci. 2005,

60, 5590.

- (14) Maestri, F.; Rota, R. Safe and Productive Operation of Homogeneous Semibatch Reactors. I: Development of a General Procedure. Ind. Eng. Chem. Res. 2006, 45, 8002.
- (15) Maestri, F.; Rota, R. Temperature Diagrams for Preventing Decomposition or Side Reactions in Liquid-liquid Semibatch Reactors. Chem. Eng. Sci. 2006, 61, 3068.
- (16) Maestri, F.; Re Dionigi, L.; Rota, R.; Lunghi, A.; Gigante, L.; Cardillo, P. Safe and Productive Operation of Homogeneous Semibatch Reactors. II: the Nitration of N-(2-phenoxyphenyl) Methane Sulphonamide. Ind. Eng. Chem. Res. 2006, 45, 8014.
- (17) Molga, E. J.; Lewak, M; Westerterp, K. R. Runaway Prevention in Liquid-phase Homogeneous Semibatch Reactors. Chem. Eng. Sci. 2007, 62, 5074.
- (18) Maestri, F.; Rota, R. Safe and Productive Operation of Homogeneous Semibatch Reactors Involving Autocatalytic Reactions with Arbitrary Reaction Order. Ind. Eng. Chem. Res. 2007, 46, 5333.
- (19) Alós, M. A.; Nomen, R.; Sempere, J. M.; Strozzi, F.; Zaldívar, J. M. Generalized Criteria for Boundary Safe Conditions in Semi-batch Processes: Simulated Analysis and Experimental Results. Chem. Eng. Process. 1998, 37, 405.
- (20) Morbidelli, M.; Varma, A. A Generalized Criterion for Parametric Sensitivity: Application to Thermal Explosion Theory. Chem. Eng. Sci. 1998, 43, 91.
- (21) Strozzi, F.; Zaldívar, J. M.; Kronberg, A. E.; Westerterp, K. R. On-line Runaway Detection in Batch Reactors Using Chaos Theory Techniques. AIChE J. 1999, 45, 2429.

- (22) Zaldívar, J. M.; Cano, J. Alós, M.A.; Sempere, J. M.; Nomen, R.; Lister, D.; Maschio, G.;
 Obertopp, T.; Gilles, E. D.; Bosch, J.; Strozzi, F. A General Criterion to Define Runaway
 Limits in Chemical Reactors. J. Loss. Prev. 2003, 16, 187.
- (23) Bosch, J.; Strozzi, F.; Zbilut, J. P; Zaldívar, J. M. On-line Runaway Detection in Isoperibolic Batch and Semibatch Reactors Using the Divergence Criterion. *Comp. Chem. Eng.* 2004, 28, 527.
- (24) Zaldívar, J. M.; Bosch, J.; Strozzi, F.; Zbilut, J. P. Early Warning Detection of Runaway Initiation Using Non-linear Approaches. *Nonlin. Sci. Num. Sim.* **2005**, *10*, 299.
- (25) Varma, A.; Morbidelli, M.; Wu, H. Parametric Sensitivity in Chemical Systems; University Press: Cambridge, 1999.



Table 1. Expressions of the reactivity enhancement factor, RE, and of the function, f, for homogeneous and heterogeneous (liquid-liquid) SBRs in which slow or fast reactions take place in the dispersed or continuous phase¹²⁻¹⁴.

Parameters:	Checks
(UA) ₀	$R_{y,calc}(t_{D,MIN,calc}) > \frac{(1 - \varepsilon \cdot S_{R_{y,QFS}/Co}) \cdot [(1 - \varepsilon) \cdot Co_{MIN,calc} + R_{H}]}{Co_{MIN,calc} + R_{H}} \cdot R_{y,QFS}(Co_{MIN,calc})$
$\Delta \tau_{ad,0}$	$R_{y,calc}(t_{D,MIN,calc}) > R_{y,QFS}(Co_{MIN,calc})$ $\varepsilon < \frac{toll}{1-toll} \cdot \frac{1}{S_{\psi/E_X}}$
Γ	$R_{y,calc}(t_{D,MIN,calc}) > \exp\left(\varepsilon \cdot \frac{\gamma_{calc}}{\tau_{cool}}\right) \cdot R_{y,QFS}(Co_{MIN,calc})$ $\varepsilon < \frac{toll}{1 - toll} \cdot \frac{1}{S_{\psi/E_X}}$
A	$R_{y,calc}\left(t_{D,MIN,calc}\right) > \frac{1}{1-\varepsilon} \cdot R_{y,QFS}\left(Co_{MIN,calc}\right)$
N	$R_{y,calc}(t_{D,MIN,calc}) > \left(C_{B,0} \cdot \frac{\nu_A}{\nu_B} \cdot m_A\right)^{\varepsilon \cdot n_{calc}} \cdot \left(1 - \varepsilon \cdot S_{R_{y,QFS}/n}\right) R_{y,QFS}(Co_{MIN,calc})$

Table 2. Checks, for heterogeneous L-L kinetically controlled SB systems, on experimental parameters subjected to a relative degree of uncertainty ε and a relative tolerance on MAT value. For each parameter, β , the relative uncertainty ε bounds the range where the real value is expected to lie in: $\beta_{calc}(1-\varepsilon) \le \beta_{real} \le \beta_{calc}(1+\varepsilon)$. Conversely, *toll* has been introduced to prevent undesirable effects due to errors in MAT estimation: its use lowers the measured value of MAT to that one used in the optimization – scale-up procedure (EMAT=MAT(1-*toll*)).

ACS Paragon Plus Environment

Sensitivity Index	<i>Co</i> <5	<i>Co>5</i>
$S_{R_{y,QFS}/Co}$	$0.0007 \cdot \frac{Co}{0.0007 \cdot Co + 0.0519}$	$\frac{-0.0241}{-0.0241 \cdot \ln(Co) + 0.094187}$
$S_{R_{y,QFS}/n}$	- 0.469	- 0.469
	$0 < E_X < 2$	$2 < E_X < 30$
S_{Ψ/E_X}	$\frac{-1 \cdot 10^{-2} \cdot E_{X}^{2} + 8.91 \cdot 10^{-2} \cdot E_{X}}{-1 \cdot 10^{-2} \cdot E_{X}^{2} + 8.91 \cdot 10^{-2} \cdot E_{X} + 1}$	$\frac{-3.72 \cdot 10^{-4} \cdot E_{X}^{2} + 2.50 \cdot 10^{-2} \cdot E_{X}}{-3.72 \cdot 10^{-4} \cdot E_{X}^{2} + 2.50 \cdot 10^{-2} \cdot E_{X} + 1.09}$

Table 3. Normalized sensitivity coefficients of $R_{y,QFS}$ and Ψ with respect to Co, n and E_X , for heterogeneous L-L kinetically controlled SB systems.

Captions to the figures.

Figure 1. Boundary diagram for the identification of excessive accumulation operating conditions in exothermic SBRs in which a reaction of the form (1) is carried out.

Figure 2. Inherently safe conditions of heterogeneous (liquid-liquid) SBRs in which single reactions of the form (1) with n=0.5 and n=1 occur. Influence of the cooling number, Co, on the $R_{y,QFS}$ parameter. R_H =1. 0.02<vA Da RE<20; 0.05< ϵ <0.6; 30< γ <45; 0.1< Δ tad,0<0.7. A) slow reaction occurring in the dispersed phase; B) slow reaction occurring in the continuous phase; C) fast reaction occurring in the dispersed phase; D) fast reaction occurring in the continuous phase.

Figure 3. Inherently safe conditions of homogeneous SBRs in which single reactions of the form (1) with n=1 and n=2 occur. Influence of the cooling number, Co, on the $R_{y,QFS}$ parameter. $R_H=1$. 0.02<vA Da RE<20; 0.05< ϵ <0.6; 30< γ <45; 0.1< $\Delta \tau ad$,0<0.7.

Figure 4. Inherently safe conditions of SBRs in which a single exothermic reaction is carried out. Influence of the exothermicity number, E_x , on the maximum temperature rise $\psi = (T_{max}/T_0)_{max}$ and graphical identification of the maximum exothermicity number, $E_{x,MAX}$, during the scale-up process. $R_H=1.2 < Co < 80; 0.75 < n < 2; m=1; 0.02 < Da < 20; 0.05 < \varepsilon < 0.6; 30 < \gamma < 45; 0.1 < \Delta \tau_{ad,0} < 0.7; R_y > R_{y,QFS}$.

Figure 5. Flow diagram for the selection of safe operating conditions at the laboratory scale and for their optimum sale-up to the industrial reactor scale.



Figure 1. Boundary diagram for the identification of excessive accumulation operating conditions in exothermic SBRs in which a reaction of the form (1) is carried out.









Figure 2. Inherently safe conditions of heterogeneous (liquid-liquid) SBRs in which single reactions of the form (1) with n=0.5 and n=1 occur. Influence of the cooling number, Co, on the $R_{y,QFS}$ parameter. R_H =1. 0.02<vA Da RE<20; 0.05< ϵ <0.6; 30< γ <45; 0.1< $\Delta \tau ad$,0<0.7. A) slow reaction occurring in the dispersed phase; B) slow reaction occurring in the continuous phase; C) fast reaction occurring in the dispersed phase; D) fast reaction occurring in the continuous phase.



Figure 3. Inherently safe conditions of homogeneous SBRs in which single reactions of the form (1) with n=1 and n=2 occur. Influence of the cooling number, Co, on the $R_{y,QFS}$ parameter. R_H =1. 0.02<vA Da RE<20; 0.05< ϵ <0.6; 30< γ <45; 0.1< $\Delta\tau$ ad,0<0.7.



Figure 4. Inherently safe conditions of SBRs in which a single exothermic reaction is carried out. Influence of the exothermicity number, E_x , on the maximum temperature rise $\psi = (T_{max}/T_0)_{max}$ and graphical identification of the maximum exothermicity number, $E_{x,MAX}$, during the scale-up process. R_H=1. 2<Co<80; 0.75<n<2; m=1; 0.02<Da <20; 0.05< ϵ <0.6; 30< γ <45; 0.1< $\Delta \tau_{ad,0}$ <0.7; R_y>R_{y,QFS}.



Figure 5. Flow diagram for the selection of safe operating conditions at the laboratory scale and for their optimum sale-up to the industrial reactor scale.