APPLICATION OF A GENERAL PROCEDURE FOR SELECTING SAFE AND PRODUCTIVE OPERATING CONDITIONS IN HOMOGENEOUS SBR TO THE NITRATION OF N-(2-PHENOXYPHENYL) METHANE SULFONAMIDE

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ABSTRACT

The safe operation of an indirectly cooled semibatch reactor in which an exothermic reaction occurs requires that the characteristic time of the coreactant dosing is much higher than the characteristic time of the chemical reaction, which results in a low accumulation of unreacted coreactant in the system. On this basis, it is possible to define a target reaction temperature to which the actual temperature-time profile can be compared, in order to build *boundary diagrams* in a suitable dimensionless space: such diagrams summarize all the possible thermal behaviors of the reactor and can be used for scaling-up the process limiting the coreactant accumulation.

However, when a maximum allowable process temperature must not be exceeded (because of safety or selectivity problems), avoiding accumulation phenomena is just a necessary, not a sufficient condition to classify as acceptable a given set of operating conditions for the reactor. Consequently, the boundary diagrams must be coupled with another typology of diagrams (called *temperature diagrams*), which allow to estimate the maximum temperature increase for a given set of operating conditions.

In this work, the method of boundary and temperature diagrams has been validated analyzing an industrial nitration process for the production of a pharmaceutical active ingredient, that is the nitration of N-(2-phenoxyphenyl) methane sulphonamide to N-(4-nitro, 2-phenoxyphenyl) methane sulphonamide, carried out in homogeneous phase in an indirectly cooled semibatch reactor, in which nitric acid is dosed over an acetic acid solution of the reactant. It has been verified through calorimetric experiments performed in a RC1 equipment that the boundary and temperature diagrams allow to safely select operating conditions characterized by a rapid nitric acid consumption, which imply a better thermal control of the reactor. Moreover, it has been shown that using the boundary and temperature diagrams method requires the knowledge of the reaction kinetics, at least in terms of a lumped expression corresponding to an optimum fitting of the experimental data.

INTRODUCTION

The thermal loss of control of batch (BR) and semibatch (SBR) reactors in which exothermic reactions are performed occurs more frequently than one could believe: in the early 90's and in the single EU country more than 100 events of this typology per year had been estimated to occur, a little number of which, fortunately, had serious consequences on the environment or in terms of human lives. However, the consequences of the single industrial accident can be so severe that the risk factor associated with such events remains very high. For these reasons the huge amount of work that in the last thirty years (from the accident of 1976 in Seveso, Italy) has been done in order to study and prevent the aforementioned phenomena is well justified. In particular, a number of criteria for the safe scale up of a process from the laboratory or pilot to the industrial scale has been developed. However, for a practical application of such criteria it must be taken into account that typically in the fine chemical and pharmaceutical industries it is often not possible to perform detailed kinetic investigations and mathematical modelling of the single process, because of the huge variety of products involved and the relatively small amount of the single productions. Such a constraint requires to the single safety criterion that wants to achieve a practical diffusion to be at the same time reliable, general and easy to use.

It is well known that the heat effects associated with a relatively fast and exothermic chemical reaction of the form $\nu_A A+\nu_B B \rightarrow C+\nu_D D$ can be better controlled by adding (at a rate dependent on the heat removal efficiency) the reactant A (usually called coreactant) to the reactant B previously charged in the reactor, that is performing the reaction in an indirectly cooled SBR operating with a sufficiently low coreactant accumulation [1]. The mass and energy balance equations for a homogeneous SBR can be written in dimensionless form as:

$$\frac{d\zeta_B}{d\vartheta} = \nu_A \, Da \, RE \; f \exp\left[\gamma\left(1-\frac{1}{\tau}\right)\right] \tag{1}$$

$$\left(1+\varepsilon\vartheta\right)\frac{d\tau}{d\vartheta} = \Delta\tau_{ad,0}\frac{d\zeta_B}{d\vartheta} - \varepsilon\left[Co\left(1+\varepsilon\vartheta\right)+R_H\right]\left(\tau-\tau_{cool}^{eff}\right) \tag{2}$$

where: ζ_B is the molar conversion of the reactant initially charged in the reactor, ϑ is the dimensionless time variable (defined assuming as a reference value the supply period), Da is the Damköhler number, related to the dosing time, RE is the reactivity enhancement factor, equal to $(\nu_B/\nu_A)^{1-n}$, f, which is equal to $[(\vartheta-\zeta_B)^n(1-\zeta_B)^m]/(1+\varepsilon\vartheta)^{n+m-1}$, is the only factor containing the functional dependence of the conversion rate on ϑ and ζ_B, γ is the activation energy in dimensionless form, R_H is the ratio between the volumetric heat capacities of the dosing stream and the reacting mixture, ε is the relative volume increase at the end of the supply period, $\Delta T_{ad,0}$ is the adiabatic temperature rise at $\vartheta=0$, Co is the cooling number, which is related to the volumetric feed rate and to the heat transfer efficiency, and τ_{cool}^{eff} is an effective cooling temperature, which takes into account the effects of both the heat removal by the coolant and the sensible heat of the dosing stream.

In the literature a number of criteria for the safe scale up of a chemical process carried out in a SBR can be found [2,3], that are based on the mathematical behaviour of the temperature and conversion time profiles. Such criteria are independent on any arbitrary definition of what an excessive coreactant accumulation is but are not always easy to use in practice, since they require the knowledge of mathematical properties of the aforementioned profiles that are often not straightforward to estimate for end users. Other criteria through an on line analysis of the reactor temperature evolution allow for an early warning detection of a runaway event [4,5] and can therefore be implemented in the control system of the reactor. The first studies for selecting safe and productive operating conditions of homogeneous SBRs in which an exothermic reaction is carried out were performed by Hugo and Steinbach [6,7] who introduced a semiempirical quantitative criterion based on the concept of coreactant accumulation in the system: in particular, as the aforementioned accumulation increases (which is the consequence of a not negligible characteristic time of the chemical reaction compared with that of the coreactant dosing) the reaction system switches from semibatch to batch like operating conditions. In such a situation, the heat removal contribution from the system can be insufficient to counteract effectively the enthalpic contribution associated with too fast and exothermic chemical reactions. For this reason, accumulation phenomena in exothermic SBRs must be limited below a threshold value, in order to keep the thermal control of the process. Few years later, Steensma and Westerterp [8-10] extended the criterion of Hugo and Steinbach to the case of heterogeneous (liquid-liquid) SBRs, introducing the concept of target temperature. Such a target thermal profile is the consequence of both a negligible characteristic time of the chemical reaction with respect to that of the coreactant dosing and of a negligible characteristic time of the heat removal from the system compared with that of the enthalpic contribution associated with the conversion rate. Such assumptions lead to the following expression of the target temperature during the supply period, that can be easily derived from the energy balance (2) for the reactor:

$$T_{ta} = T_0 + 1.05 \frac{\Delta T_{ad,0}}{\varepsilon\left[Co\left(1+\varepsilon\vartheta\right)+R_H\right]} \tag{3}$$

The 5% overestimation of the T_{ta}-T_0 difference in expression (3) has been firstly introduced by Steensma and Westerterp [8] in order to account for the deviation of the operating conditions of a real SBR from the ideal situation of no coreactant accumulation. Through a comparison between the target and the actual temperature time profiles it is possible to classify the reactor thermal behaviour from the safety point of view and to generate on this basis boundary diagrams which, in a suitable dimensionless space that can be derived from the energy balance (2) of the reactor, separate inherently safe and excessive accumulation operating conditions. Such a dimensionless space is given by an exothermicity number, E_x, that contains the information about the reaction enthalpy and a reactivity number, R_y, which is related to the initial dependence of the conversion rate on temperature. These parameters can be computed through the following generalized expressions:

$$E_x = \frac{\gamma_{app}}{\tau_{cool}^2} \frac{\Delta\tau_{ad,0}}{\varepsilon\left(Co+R_H\right)} \tag{4}$$

$$R_y = \frac{\nu_A \, Da \, RE \exp\left[\gamma_{app}\left(1-1/\tau_{cool}\right)\right]}{\varepsilon\left(Co+R_H\right)} \tag{5}$$

In Figure 1, an example of boundary diagram is reported, from which the following operating regions of an indirectly cooled SBR can be recognized increasing the value of the initial reaction temperature (which is assumed to be equal to the coolant temperature and to the dosing stream temperature under isoperibolic conditions):

1) for sufficiently low values of the coolant temperature, the peak reaction temperature attained is lower than the local target value: this means that the reaction is not ignited. In such a situation the accumulation of the coreactant in the system reaches obviously high values but the characteristic time of the reaction is never low enough to cause the thermal loss of control of the system;
2) as the coolant temperature increases, the maximum temperature “pinches” locally the target line: this situation is referred to as a marginal ignition;
3) increasing further the coolant temperature, the characteristic time of the reaction is at the same time not so low to limit the accumulation of the coreactant and not so high to avoid -when the reaction itself ignites- the loss of control of the system from the thermal point of view. This situation implies maximum reaction temperatures higher than the local target value and corresponds to excessive accumulation operating conditions;
4) as the coolant temperature still increases, the characteristic time of the reaction becomes low enough to limit the accumulation of the coreactant A in the system, so that no exceeding of the target temperature can occur. The minimum coolant temperature for which the exceeding of the local target value by the maximum reaction temperature disappears is referred to as a QFS (Quick onset, Fair conversion, Smooth temperature profile) situation [8], because it is characterized by a temperature evolution which quickly approaches the target line and remains close to it throughout the dosing period, at the end of which the conversion ζ_B is almost complete.

The boundary line represented in Figure 1 separates the excessive accumulation region (inside the line itself), the no ignition region (for low R_y values), the QFS region (for high R_y values) and the inherently safe region (for either E_x values lower than $E_{x,MIN}$ or R_y values higher than $R_{y,QFS}$).

The boundary diagrams can be employed to solve two typologies of problems:

1) identify for an existing SBR thermally safe operating conditions, that is operating conditions characterized by a sufficiently low coreactant accumulation;

2) scale up a given set of safe operating conditions for a SBR from the laboratory or pilot to the industrial scale, without solving the mathematical model of the reactor.

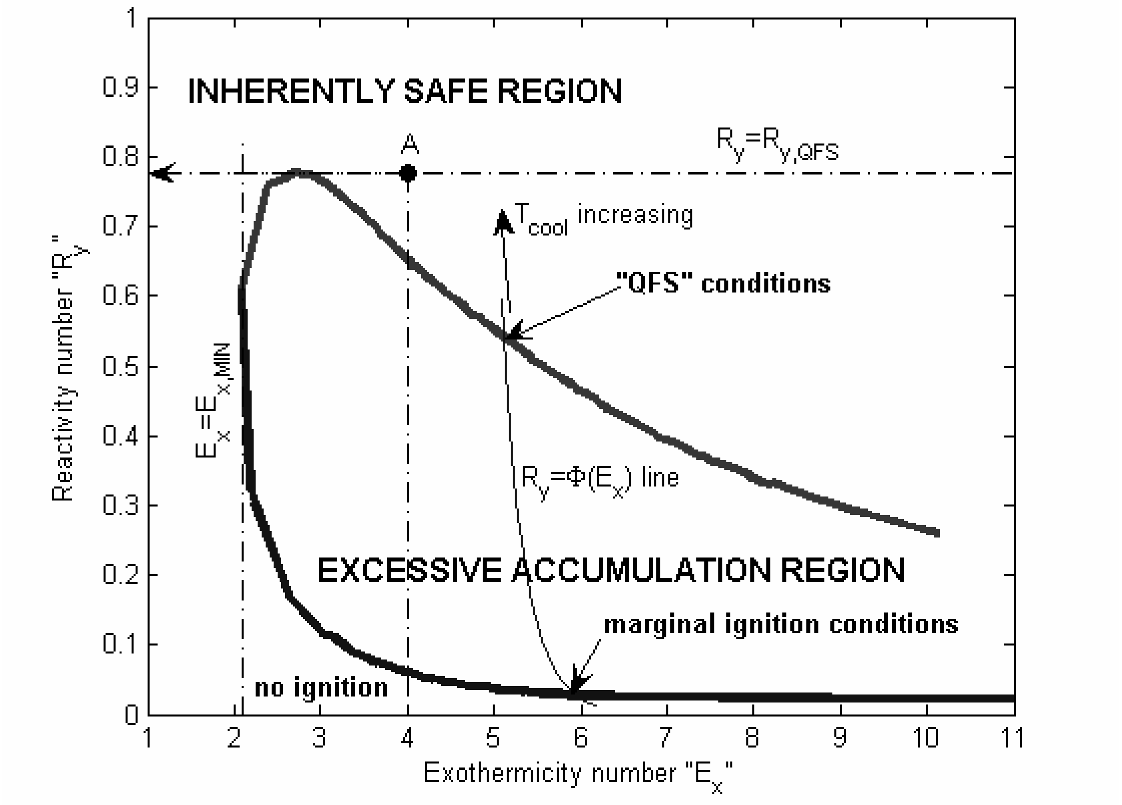

Figure 1 Different thermal behavior regions for an indirectly cooled SBR represented through the boundary diagram.

For homogeneous SBRs a number of safety criteria developed for (1,1) order reactions can be found in the literature [6,7,11]. However, the calorimetric experimental data are usually fitted through power law type rate expressions with reaction orders different from (1,1). Consequently, the model discussed for heterogeneous (liquid-liquid) SBRs [12,13,14] has been extended to the homogeneous reaction case, developing the corresponding expressions of the parameters involved as well as of the dimensionless space for the representation of the diagrams (that is, the E_x and R_y parameters).

RESULTS AND DISCUSSION

A number of boundary diagrams has been generated for several sets of the parameters involved (that is: Co, R_H, n and m). It has been found that, as required by the criteria reported in the literature, when dealing with homogeneous semibatch reactions of (1,1) orders a given set of operating conditions can be considered safe if it implies R_y values higher than one. However, for other values of the reaction orders, this safety criterion does not hold anymore.

As can be deduced from Figure 2, where boundary diagrams for various operating parameters are represented, and from the results reported in Table 1, that summarizes the values of the sensitivity coefficients with respect to the main operating parameters, also in the homogeneous case using boundary diagrams calculated for different (n,m) values than the real ones can lead to strongly unsafe or low production operating conditions.

However, as a significant difference with respect to the heterogeneous (liquid-liquid) case [12,13,14], it has been found that if the n value according to which the diagram has been calculated is lower than the real value, the conclusions drawn can be unsafe. Such an opposite behavior between homogeneous and heterogeneous (liquid-liquid) SBRs can be explained analyzing the time evolution of the coreactant accumulation in the two cases.

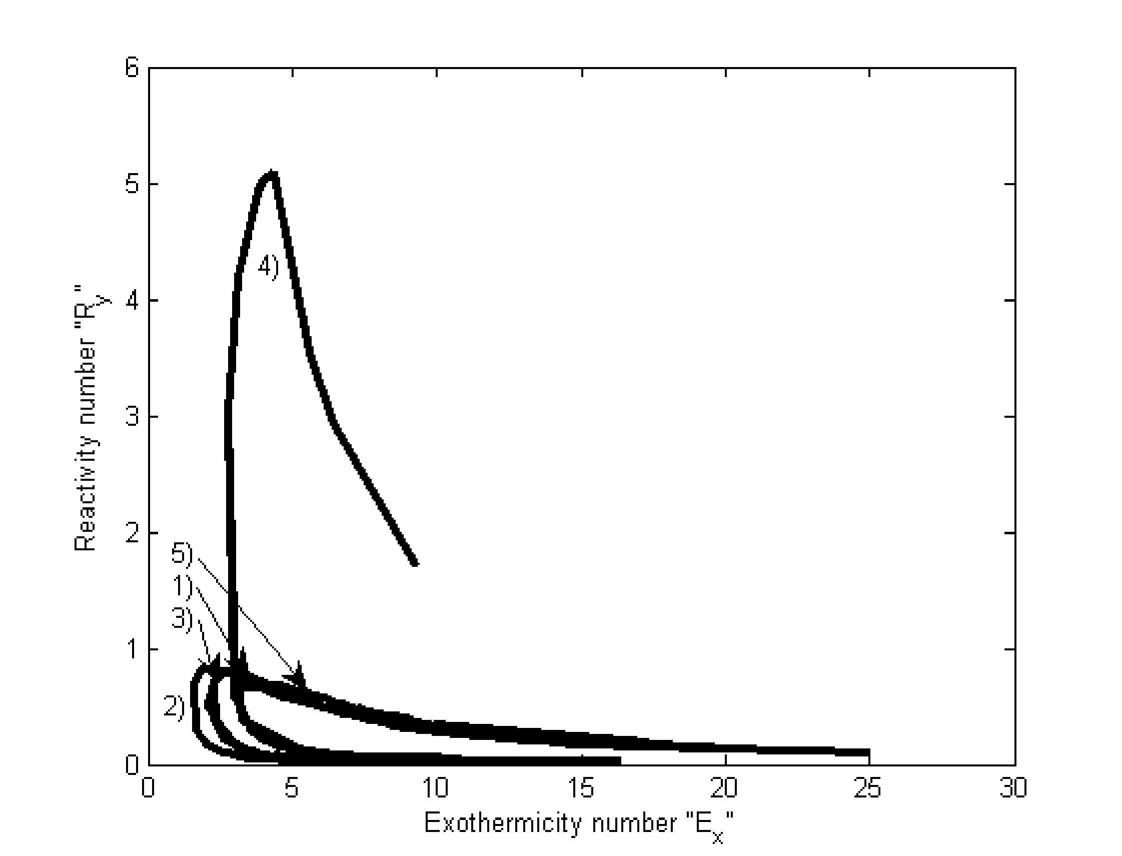

Figure 2 Sensitivity of the boundary diagrams for homogeneous semibatch reactions with respect to the model parameters. $0.02<\nu_A$ Da RE<20, $0.05<\varepsilon<0.6$, $30<\gamma<45$, $0.1<\Delta\tau_{ad,0}<0.7$. 1) Co=10, R_H=1, n=1, m=1; 2) Co=20, R_H=1, n=1, m=1; 3) Co=10, R_H=2, n=1, m=1; 4) Co=10, R_H=1, n=2, m=1; 5) Co=10, R_H=1, n=1, m=2.

Moreover, also in the homogeneous case if the reaction order of the reactant initially loaded in the reactor, m, changes the approximated boundary diagram or safety criterion can in general be used, since the sensitivity of the $E_{x,MIN}$ and $R_{y,QFS}$ values with respect to the parameter m is relatively low. Finally, because of the significantly different sensitivities of $E_{x,MIN}$ and $R_{y,QFS}$ to n and m, the global reaction order cannot be used as a discriminating parameter in order to establish whether a boundary diagram or safety criterion developed for given reaction orders can be used for the safety analysis of a system involving different values of these parameters.

Table 1 Normalized sensitivity coefficients of $R_{y,QFS}$ and $E_{x,MIN}$ with respect to the Co, R_H, n and m parameters.

	Co	**R_H**	**n**	**m**
$R_{y,QFS}$	0.032	$9.7\cdot10^{-4}$	5.376	0.154
$E_{x,MIN}$	0.295	0.075	0.232	0.401

Also the temperature diagrams method [14] has been extended to homogeneous reaction systems: an example of temperature diagram for a homogeneous SBR is presented in Figure 3. When selecting a set of operating conditions for a homogeneous SBR, the corresponding temperature diagrams can firstly be used to verify that during the normal reactor operation no exceeding of the maximum allowable temperature (MAT) can occur. Subsequently, the related boundary diagrams can be used to prevent excessive coreactant accumulation, that can become dangerous during upset conditions.

The method developed for the prediction of safe and productive operating conditions of homogeneous SBRs has been then validated using, as a test case, the final reaction step for the production of a pharmaceutical active ingredient, that is the nitration of N-(2-phenoxyphenyl) methane sulfonamide (FAM) to N-(4-nitro, 2-phenoxyphenyl) methane sulfonamide (NIM). Such a reaction is performed in homogeneous phase in indirectly cooled SBRs, in which nitric acid is added to an acetic acid solution of the reactant to be nitrated.

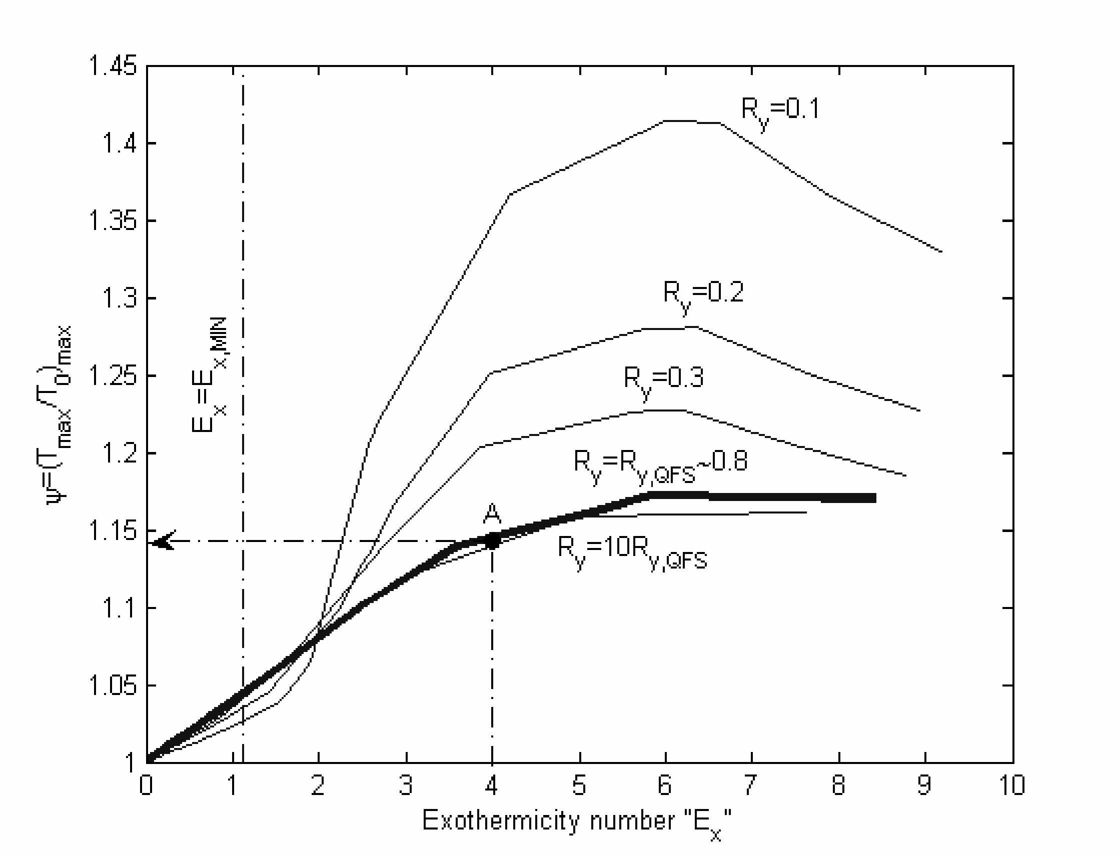

Figure 3 Temperature diagram for the determination of the peak reaction temperature in a homogeneous SBR.

It is well known that nitration reactions can be critical from the safety point of view, since an excessive nitric acid accumulation in the system can trigger consecutive oxidations of the reaction products and, as a final consequence, strongly exothermic decompositions of the reacting mixture.

A preliminary characterization of the thermal stability of the species involved as well as of the reaction mixture has been performed through the software CHETAH of ASTM [15] and experimentally verified through DSC measurements, leading to the conclusion that the most critical situation involves a strongly exothermic decomposition event of the final reacting mixture at 210°C. However, since the reaction is carried out at the industrial scale at atmospheric pressure, the solvent boiling point (equal to 120°C) represents the maximum allowable temperature for the process in question.

A kinetic characterization of the production reaction performed through adiabatic (Phi-TEC II) and further verified through isoperibolic (RC1) experiments [16], results in values of the reaction orders of the dosed coreactant (that is, nitric acid) and of the reactant initially charged in the reactor (that is, FAM) equal to 2 and 0.2, respectively.

To select safe and productive operating conditions for the process the boundary and temperature diagrams have been used and their predictions have been validated through a number of RC1 experiments. In particular, 11 experiments have been carried out changing feeding time and coolant temperature. Only 3 of 11 experiments (labeled as 5a, 7a and 12a) were located inside the Excessive accumulation Region.

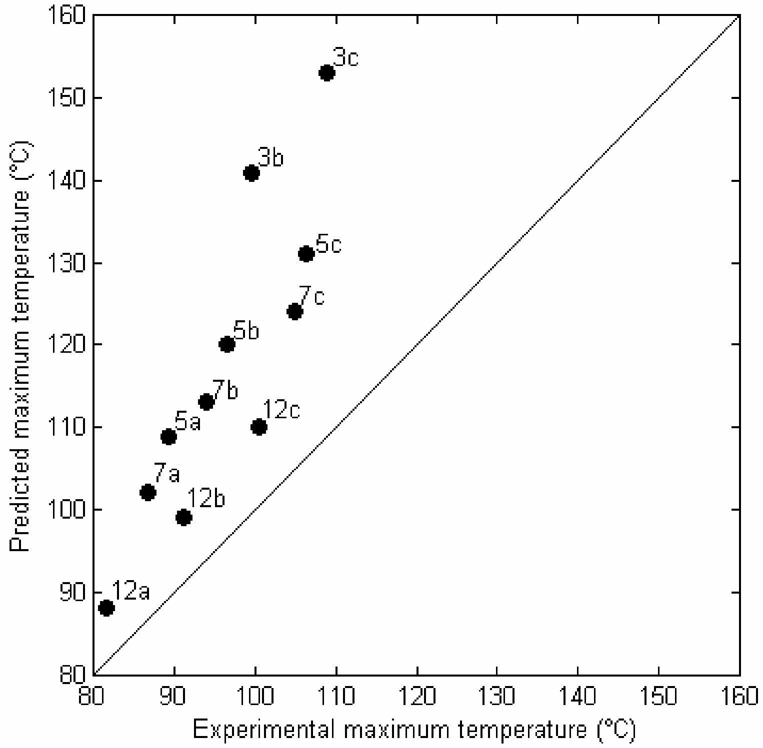

Figure 4 Parity plot for the comparison of the experimental maximum temperatures reached and the corresponding values predicted through the temperature diagrams.

In Figure 4, the predictions of the temperature diagrams have been compared with the corresponding experimental values: as it is evident, the temperature diagrams always overestimate the maximum temperature. This is not only a welcome feature since it provides conservative estimations but it follows from the procedure used to build the diagrams. For a given couple of E_x and R_y values, the temperature diagrams provide the maximum achievable value of the peak temperature among all the possible combinations of the dimensionless parameters characterizing the SBR dynamics. This means that the particular combination of such parameters representing the system under examination can be the one providing the maximum peak temperature, but most probably it is not. In this case, the experimental temperature will be lower than that predicted through the temperature diagrams. In any case, the experimental maximum temperature can never be higher than the value predicted through the temperature diagrams, coherently with the findings summarized in Figure 4. Moreover, it should be noticed that predicted temperature values higher than the reaction mixture boiling point means only that the MAT is exceeded, since the mathematical model does not account for solvent evaporation. However, this is not a problem since disregarding solvent evaporation leads to conservative results in terms of maximum achievable temperature. We can also note from Figure 4 that all the main experimental trends are correctly predicted by the temperature diagrams. For instance, the values of the maximum temperature for the experiments performed at the same initial temperature decrease with increasing the dosing time (runs 3→5→7→12 with the same letter in Figure 4) as well as it decreases by decreasing the initial temperature at the same dosing time (runs c→b→a with the same number in Figure 4). The predictions of the boundary diagrams have been analogously validated with respect to the experimental values of the relative coreactant amount at the end of the dosing time: operating conditions characterized by (E_x,R_y) values located inside the excessive accumulation region imply higher values of the aforementioned quantity.

Coherently, we can see from Figure 5 that all the experimental runs belonging to the inherently safe region imply values of the relative coreactant amount in the range 10÷15%, whereas the three runs characterized by operating parameters located inside the excessive accumulation region imply relative coreactant amounts close to 25%.

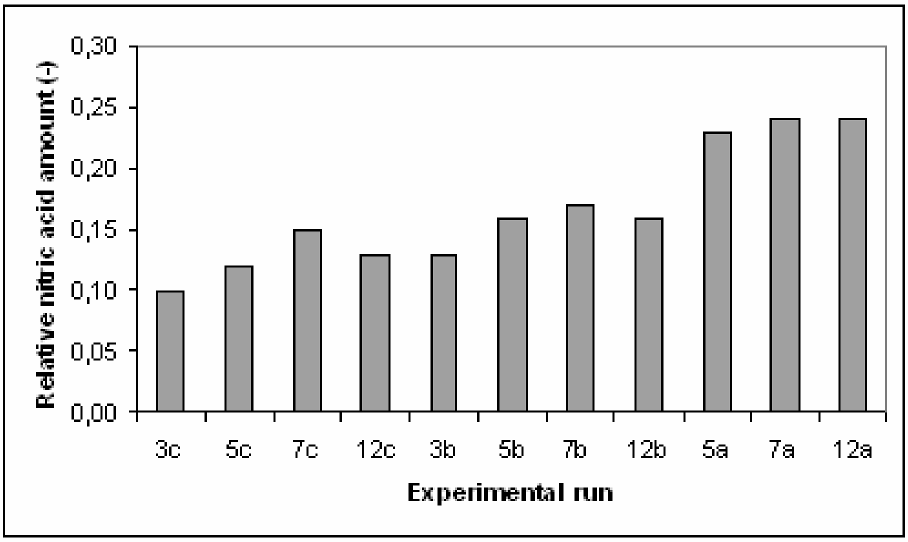

Figure 5 Experimental values of the relative coreactant amount at the end of the dosing period.

According to the rules of thumb for the safe use of diagrams calculated for approximated values of the parameters involved, the same conclusions have been drawn using boundary and temperature diagrams calculated for R_H=1 and m=1, because of the relatively low sensitivity of the location and extension of the diagrams themselves on the R_H and m values. On the contrary, it has been verified that uncontrolled approximations on the reaction order of the dosed coreactant lead to unreliable conclusions. Forcing n=m=1 in the fitting procedure of the Phi-TEC II data the difference between the R_y values calculated according to the two sets of reaction orders (that is n=2, m=0.2 and n=m=1 respectively) is much lower than the corresponding difference between the $R_{y,QFS}$ values: in particular, for the experiments performed at 68°C R_y varies approximately between 6 (for n=2, m=0.2) and 7 (for n=m=1), whereas $R_{y,QFS}$ undergoes an order of magnitude variation, ranging from 9 (for n=2, m=0.2) to 0.7 (for n=m=1).

In other words, a-priori constraints on the reaction orders followed by a correspondent adjustment of the remaining kinetic parameters (that is the pre-exponential factor and the activation energy) in order to fit the experimental data, typically lead to minor changes in the R_y values, but to significant variations in the $R_{y,QFS}$ values: however, since the classification of a given set of operating conditions from the safety point of view arises from a comparison between the R_y and $R_{y,QFS}$ values, it is clear that the aforementioned assumptions can lead to unreliable results. For the sake of example, in Figure 6 the (E_x,R_y) points for the experiment performed at T_0=68°C and t_D=12' (that is, for the maximum tested value of the dosing time) have been represented together with the related boundary diagrams, according to the two aforementioned sets of kinetic parameters. As can be observed, the constraint n=m=1 in the fitting of the calorimetric data results in a (E_x,R_y) point belonging to the inherently safe region of the corresponding diagram, representing operating conditions characterized by a low nitric acid accumulation in the system. The same results can also be obtained through the safety criterion of Hugo et al. [6,7,11] for homogeneous (1,1) order reactions, according to which operating conditions implying R_y values higher than one can be considered safe. However, such conclusions do not agree with the experimental results and with the predictions of the method in question without uncontrolled constraints on the reaction order of the dosed coreactant, thus confirming that when using boundary and temperature diagrams such approximations can lead to unsafe conclusions.

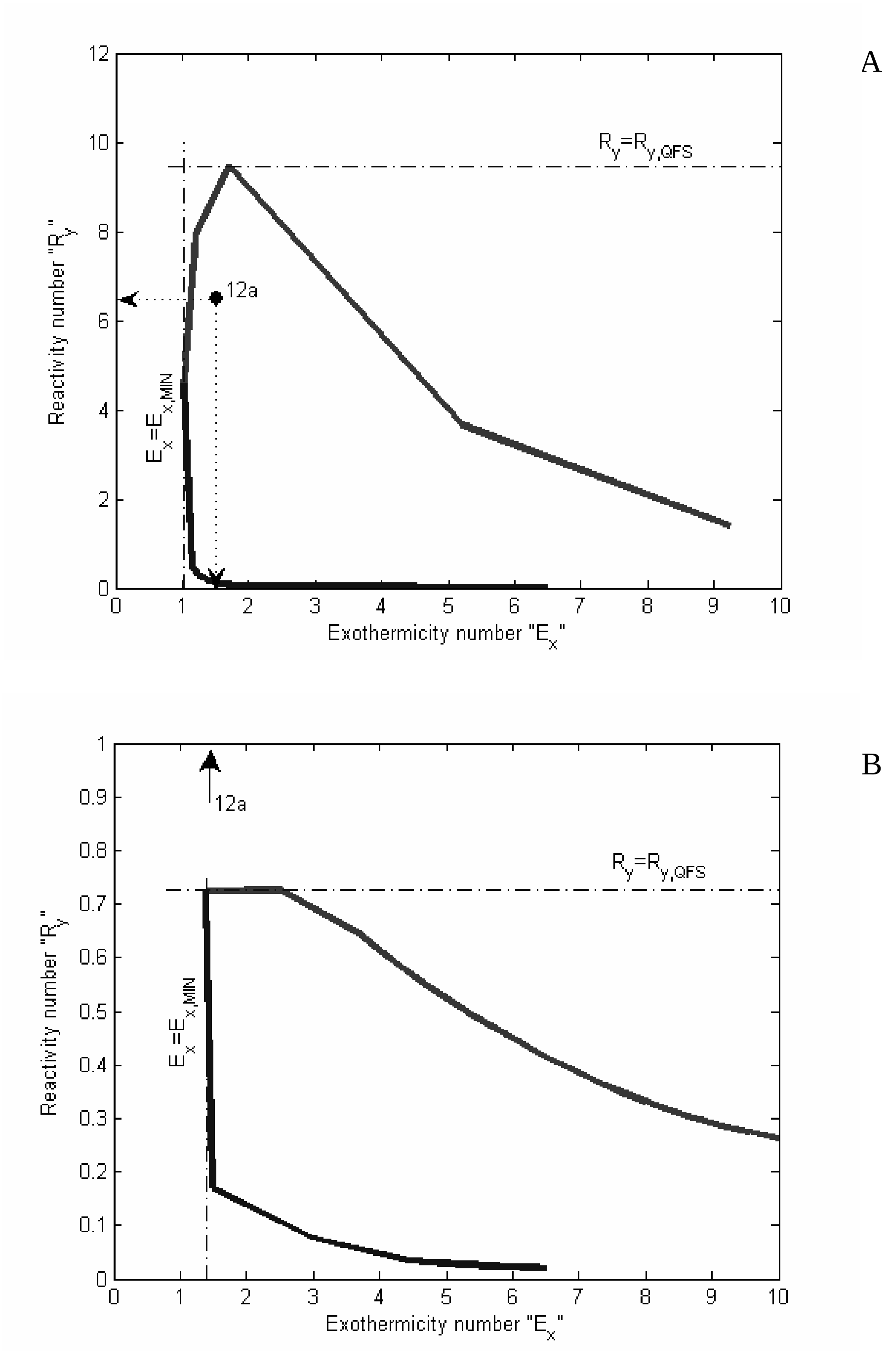

Figure 6 Safety characterization of the operating conditions with t_D=12min and T_0=68°C through the boundary diagrams. A) Co=50, R_H=1.4, n=2, m=0.2. B) Co=50, R_H=1.4, n=1, m=1. $0.02<Da<20$, $0.05<\varepsilon<0.6$, $30<\gamma<45$, $0.1<\Delta\tau_{ad,0}<0.7$ (T_R=303K).

It can be finally noticed that the method of boundary and temperature diagrams can be regarded as a useful tool for selecting with a minimum experimental effort safe and productive operating conditions of SBRs in which exothermic reactions are performed, since they allow for a planning of the experimental activity (that is, of the RC1 experiments) through a rapid a priori screening of the operating conditions.

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