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Safe Intensification of Potentially Runaway Reactions: from Semibatch to Continuous Processes

Sabrina Copelli*[a], Marco Barozzi[a], Francesco Maestri[b], Renato Rota[b]

[a]Università degli Studi dell'Insubria, Dpt. of Scienza e Alta Tecnologia, via G. B. Vico 46, 21100 Varese, Italy
[b]Politecnico di Milano, Dpt. of Chimica, Materiali e Ingegneria chimica "G. Natta", piazza Leonardo da Vinci 22, 20133 Milano, Italy
sabrina.copelli@uninsubria.it

Fast and highly exothermic reactions are commonly carried out in semibatch reactors (SBRs) in order to better control the heat evolution by the feeding rate. In fact, for such processes, a phenomenon known as "thermal runaway", that is an uncontrolled reactor temperature increase, may be triggered whenever the rate of heat removal becomes lower than the rate of heat release. This dangerous temperature increase, occurring in practically adiabatic conditions, can trigger secondary undesired exothermic reactions or, in some cases, the decomposition of the whole reacting mixture with consequent reactor pressurization and, eventually, explosion followed by the release of high amounts of hazardous products. As a consequence, several studies on the detection of the so called "runaway boundaries" have been performed during years.

However, from a practical perspective, the desired goal of whatever enterprise is to attain the maximum productivity maintaining safe conditions. Such a goal can be achieved using a series of continuous stirred tank reactors (CSTRs) operated in the isothermal temperature control mode; but a possible change of the reactor type, from discontinuous (e.g. batch or SB) to continuous (series of CSTRs), with the aim of increasing the productivity cannot be performed so easily when a potentially runaway process is involved.

The main aim of this work has been to compute the number of CSTRs in a series that, guaranteeing the requested productivity and reactants conversion under safe operating conditions (runaway phenomena cannot be triggered), minimizes the volume of each reactor of the series. Such a number results to be a function of the employed kinetic scheme and the dosing policy of the co-reactants. In this work, two different dosing policies (1- co-reactant dosed into the first reactor of the series; 2) co-reactant dosed into the first NR-1 reactors of the series) will be analyzed for the relevant case study of the synthesis of N-(4-nitro, 2-phenoxyphenyl) methane sulphonamide. The obtained results have shown that it is possible to increase the overall productivity of the process, simply shifting from discontinuous to continuous operating mode, also achieving a safe intensification, that is, having lower reacting volumes at the full plant.

1. Introduction

In pharmaceutical and fine chemical industries, extremely fast and exothermic reactions have to be conducted in order to produce a wide variety of valuable products. Such reactions can trigger a phenomenon known as "thermal runaway", that is a loss of the temperature control of the synthesis reactor associated with the fact that the rate with which the cooling system is able to remove the heat generated is lower than that at which the heat is released by the reaction itself.

In order to partially control the extent of the heat release, these processes are usually carried out using semibatch (SB) reactors in which one or more reagents are dosed on a previously loaded mixture.

Following the more and more pressing request to obtain a greater productivity to maintain the competitiveness of the desired product on the market, process engineers and researchers have tried to find optimization criteria able to both maintained safe operating conditions and achieved the maximum possible productivity (Maestri et al., 2009; Copelli et al., 2010; Copelli et al., 2011; Copelli et al., 2012; Maestri and Rota, 2016 a and b). This, for a SBR, means that the minimum safe value of the dosing time has to be determined.

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Another alternative solution could be the exploration of the possibility of using different types of reactor from SB in order to make synthesis that, in the past, were carried out only using semibatch reactors (essentially for safety reasons). Therefore, following the purpose of eliminating the dead times of a synthesis, the first and simplest solution that has been proposed was to use a series of continuous reactors as CSTRs (acronym for "Continuous Stirred Tank Reactors"). In a series of CSTRs, in fact, with the exception of start-up times and special stops due to failure or malfunctioning, the desired product is dispensed continuously allowing both a remarkable increase in productivity (even of one order of magnitude when pursuing a sufficient process intensification) and an uniformity in the product quality (there are no production lots). Also, making a synthesis in continuous reactors substantially eliminates the problem of optimization, which is always present whenever discontinuous reactors are employed for a synthesis. In fact, it is sufficient to choose the required productivity and search for a reaction volume able to guarantee an appropriated residence time for the completion of the desired reactions. However, it remains extremely relevant the problem of safety during the start-up phase of an exothermic system because fluctuations in the reactors liquid level may trigger runaway phenomena. This implies that any set of optimal operating parameters that is proposed for a continuous potentially runaway system must be then checked from the point of the thermal stability of the process before being approved.

Summarizing, three constraints must be necessarily fulfilled in order to obtain a safe optimization of a continuous process involving potentially runaway reactions: 1) the productivity must be equal to (or major of) a determined P value [kmol / h]; 2) the conversion to the desired product must be higher than a fixed ζ_{min} value; and 3) the temperature inside of each reactor must be kept lower than a critical value (that it can be calculated from the experimental Maximum Allowable Temperature (MAT) value which can be the onset temperature beyond which the self heating rate of the reacting mass exceeds 0.02 °C/min in an Accelerating Rate or PHI-TEC II like Calorimeter, as well as any other temperature threshold arising from the process chemistry).

The main aim of this work has been to compute the number of CSTRs in a series that, complying with all the previously listed constraints, minimizes the volume of the reactors (in this work considered equal for each reactor of the series). Of course such a number will be a function of the employed kinetic scheme and the dosing policy. Therefore two different dosing policies (tested for the synthesis of N-(4-nitro, 2-phenoxyphenyl) methane sulphonamide; also note as nimesulide, NIM) will be analyzed in this work: 1) all the co-reactant dosed at the first reactor of the series; 2) splitting of the co-reactant dosing stream among the first (NR-1) reactors of the series. Results have shown that such an approach is very promising because it is possible to increase the overall productivity of the process, simply shifting from discontinuous to continuous operating mode, also achieving a safe intensification, that is, having lower reacting volumes at the full plant scale (this corresponds to safer processes as the heat removal efficiency of an installed cooling equipment is known to be higher as the reactor volume becomes lower).

2. Case Study

Statistics have shown that nitrations are among the chemical processes most frequently involved in accidents (Cardillo, 1998). This is because the nitric acid can, in certain conditions, oxidize most of the organic molecules with the development of large quantities of gases, often toxic, that can cause an explosion or even a detonation. This behavior occurs generally at high temperatures and it is favored by the presence of accumulation of nitric acid during the synthesis, which increases the rate of oxidation with greater heat production per unit of time: therefore, the consequences of a possible thermal runaway can be particularly drastic. Nitrations are highly exothermic reactions whose heat of reaction is about 120-150 kJ mol^{-1}, even if the exothermicity varies depending on the compound considered. The reaction mechanism is different depending on the reagents used; however, the most widely accepted mechanism for aromatic hydrocarbons (ArH) provides for the formation of the nitronium ion (NO_2^+) with its subsequent addition to the aromatic ring to form a complex that successively decomposes to the nitroderivative.

In this work, it will be presented, as relevant case study of potentially runaway reaction, the nitration of N-(2-Phenoxyphenyl) methane sulphonamide (FAM) to N-(4-nitro, 2-phenoxyphenyl) methane sulphonamide (NIM) that, industrially, it is carried out in an indirectly cooled SBR (nominal volume, 12.5 m^3) where a 65% w/w nitric acid aqueous solution is added to a 20% w/w acetic acid solution of FAM, previously loaded in the reactor (see Table 1 for the recipe).

Table 1: Industrial recipe for the nitration of FAM

	FAM	HNO3, 65% w/w	Acetic Acid (glacial)
Mass (kg)	1425.5	560	6813
Molecular Weight (kg kmol^{-1})	263.3	33.66	60.05

Such a reaction can be industrially performed either with or without sulfuric acid, due to the activated structure of the substrate to be nitrated: in this work, the nitration without sulfuric acid has been considered (Maestri et al., 2006). Under industrial operating conditions, the kinetic scheme for this process can be represented by the following reaction occurring in homogeneous phase:

$$FAM + HNO_3 \rightarrow NIM + H_2O \tag{1}$$

Due to the chemical structure of the substrate, there is more than one site that could be nitrated, even if the desired position (that is, the position "4" with respect to the methane-sulphonamido group) is kinetically mostly favored: this is the reason because the reaction is industrially performed in SBRs, regardless of its thermal properties (Maestri et al., 2006). Carrying out the reaction under batch conditions (and hence with a necessarily high nitric acid accumulation) would lead to increase the amount of the undesired byproducts (which are typical impurities of this process), thus lowering the process selectivity and complicating the subsequent purification steps (Maestri et al., 2006).

Since this reaction has been widely analyzed (from both the thermochemical and kinetic point of view) elsewhere (Maestri et al., 2006), here only a few properties will be listed in Table 2.

Table 2: Most relevant process parameters for the nitration of FAM

Parameter	Value	Parameter	Value
Reacting mixture mean specific heat capacity, J kg^{-1} K^{-1}	2167	Heat of reaction, J $kmol^{-1}$	1.27e8
Maximum Allowable Temperature, MAT (PHI-TEC II detection), K	393	Adiabatic temperature increase, ΔT_{ad}, K	38.5

The reaction is carried out industrially in a semibatch reactor of 12.5 m^3, operating in the isothermal temperature control mode (process set-point temperature is 80 °C), by dosing the nitric acid in a time equal to about 2 h. In these conditions, the total conversion of FAM to NIM is obtained, the temperature can be maintained in a range of ±5 °C with respect to the set point value and a productivity P of about 215 kg_{NIM} h^{-1} is assured (note that the total process time is about 400 min and it comprises all dead times such as reactor loading and unloading plus cleaning).

In response to a hypothetic request for doubling the productivity of the desired product (NIM), P_{set}, it can be decided to evaluate the possibility to operate the process in continuous mode using a series of NR CSTRs, taking care to maintain the same process set-point temperature in order to avoid both changes in the characteristics of the desired product and the triggering of secondary reactions. Pursuing the goal of intrinsic safety, that is reducing as much as possible the reaction volumes (consistently with the fact that it must be ensured a sufficient contact time within the reactor for the desired reaction to occur) in order to increase the effectiveness of the heat exchange during the synthesis (this is a very important aspect when treating with a potentially runaway process), it is necessary to determine the number of reactors in the series that minimizes the reactors volume (considered equal for each reactor of the series) also satisfying the following constraints:

$$P = P_{set} \tag{2}$$

$$\zeta_{end} \geq \zeta_{\min}(99.0\%) \tag{3}$$

$$\zeta_{\max} \cdot \Delta T_{ad} < MAT \tag{4}$$

where ζ_{end} is the conversion obtained at the outlet of the reactors series and $\zeta_{\max}$ is the relative conversion obtained in the first reactor of the series. In the optimization algorithm, the search for the minimum volume of the reactors is subjected to a condition: when two conversion values satisfy Eq(3), if there is a conversion corresponding to a slightly larger volume but lower number of reactors in the series, such a value is selected.

3. Mathematical Model

Since the constitutive equations for a homogeneous semibatch reactor have been extensively discussed elsewhere (Maestri et al., 2006), here only the dimensionless material balance equation will be reported (isothermal operating conditions have been assumed):

$$\frac{d\zeta}{d\tau} = k_\infty \cdot \exp\left(-\frac{E_{att}}{RT}\right) \cdot [B]_0^{(\alpha+\beta-1)} \cdot t_{dos} \cdot (\lambda)^\alpha \cdot \frac{\left(\tau - \frac{1}{\lambda} \cdot \zeta\right)^\alpha \cdot (1-\zeta)^\beta}{(1+\varepsilon \cdot \tau)^{\alpha+\beta-1}} \qquad (5)$$

$$I.C. \qquad \tau = 0 \Rightarrow \zeta = 0$$

where: α and β are the reaction orders, $k = k_\infty \cdot \exp(-E_{att}/RT)$ is the kinetic constant of the reaction, $[B]_0$ is the initial concentration of species B (in this case, FAM), t_{dos} is the dosing time, λ is the stoichiometric excess of A (nitric acid) with respect to B (FAM), τ is the dimensionless time, ζ is the conversion and $\varepsilon = V_{dos}/V_0$ is the ratio between the dosed and the initially loaded volume.

Such an equation can not be solved analytically despite the isothermal condition hypothesis, therefore we can only describe the productivity of the system referring to its solution at the time $t_{end} = t_{dos} + t_{batch}$, ζ_{end}:

Defining the productivity *P* of the SBR as:

$$P = \frac{[B]_0 \cdot V \cdot \zeta_{end}}{(t_{dos} + t_{batch} + t_{dead})} \qquad (6)$$

we can notice that it is a function of the conversion at the end of each single batch, the reactor volume and, the dosing, batch and dead times of the batch. In order to increase the productivity we need to either increase the reactor volume or reduce the dosing time: of course when facing a potentially runaway reaction, such operations can not be performed so easily and suitable optimization criteria must be used (Maestri et al., 2009; Copelli et al., 2010). The result is that there is a physical limit under which the dosing time can not be reduced because of runaway problems (on the contrary, the batch time cannot be considered as an operating parameter since it must be chosen in order to maximize ζ_{end} without exceeding reasonable reaction times).

As said before, in order to face the problem of increasing the productivity of a potentially runaway synthesis maintaining safe conditions, the solution of changing the reactor type from SB to a series of CSTRs would permit to:

1) reduce the reaction volumes because there is a continuous production (dead times are substantially deleted);
2) take under control the violence of the reaction exothermicity (heat power released) because a CSTR operates under low reactant concentrations for all the process duration (this consideration is true when a perfect level control is maintained);
3) obtain a good degree of conversion thanks to the presence of NR CSTRs.

Considering a series of NR CSTRs at stationary conditions, where a single reaction of the same type previously considered for the SBR takes place, we can write the material balance for the n-th reactor referring to the species A (in this case, FAM) as:

$$0 = \dot{V}_{out,n-1} \cdot [A]_{n-1} - k_\infty \cdot \exp\left(-\frac{E_{att}}{RT_n}\right) \cdot [A]_n^\alpha \cdot [B]_n^\beta \cdot V_n - \dot{V}_{out,n} \cdot [A]_n \qquad (7)$$

where: $\dot{V}_{out,n-1}$ is the volumetric flow rate exiting from the (n-1)-th reactor, [m^3/s]; $\dot{V}_{out,n}$ is the volumetric flow rate exiting from the n-th reactor, [m^3/s]; T_n is the temperature inside the n-th reactor, [K]; $[\ ]_n$ are the molar concentrations inside the n-th reactor, [kmol/m^3]; V_n is the volume of the liquid phase inside the n-th reactor, [m^3].

Introducing the relative conversion of species A inside the n-th reactor of the series:

$$\zeta_{A,n} = \dot{V}_{out,n-1} \cdot [A]_{n-1} - \dot{V}_{out,n} \cdot [A]_n \Big/ \left(\dot{V}_{out,n-1} \cdot [A]_{n-1} \right) \tag{8}$$

it is possible to express the concentrations of species A exiting the various reactors as:

$$[A]_n = \dot{V}_{out,0} \cdot [A]_0 \cdot \prod_{i=1}^{n} \left(1 - \zeta_{A,i}\right) \Big/ \dot{V}_{out,n} \tag{9}$$

Considering the stoichiometric constraint between species A and B (in this case, nitric acid):

$$\zeta_{B,n} = \zeta_{A,n} \cdot \alpha_n \tag{10}$$

where:

$$\alpha_n = \dot{V}_{out,n-1} \cdot [A]_{n-1} \Big/ \left(\dot{V}_{out,n-1} \cdot [B]_{n-1} + \dot{V}_{in,n} \cdot [B]_{in,n} \right) \tag{11}$$

is the ratio between the molar flow rate of A and B entering the n-th reactor, [-]. It is important to specify that the term $\dot{V}_{in,n} \cdot [B]_{in,n}$ (molar flow rate of species B) can be present or not according to the dosing policy of the CSTRs series: in fact, if B is dosed “pure” only in the first reactor of the series, such a term must be neglected for the computation of all α_n with n>1; otherwise, such a term must be taken into account. Therefore:

$$[B]_n = \left(\dot{V}_{out,n-1} \cdot [B]_{n-1} + \dot{V}_{in,n} \cdot [B]_{in,n} \right) \cdot \left(1 - \alpha_n \cdot \zeta_{A,n}\right) \Big/ \dot{V}_{out,n} \tag{12}$$

The global conversion (at the CSTRs series outlet) can be calculated as:

$$\zeta_{end} = 1 - \prod_{i=1}^{NR} \left(1 - \zeta_{A,i}\right) \tag{13}$$

Analogously to the semibatch case, we can define a productivity *P* as:

$$P = \dot{V}_{out,0} \cdot [A]_0 \cdot \left(1 - \prod_{i=1}^{n} \left(1 - \zeta_{A,i}\right) \right) = \dot{V}_{out,0} \cdot [A]_0 \cdot \zeta_{end} \tag{14}$$

The optimum number of CSTRs in the series (NR) and the volume of each reactor (V) can be determined iteratively by superimposing the value of both ζ_{end} and P (that is, $\dot{V}_{out,0}$ = volumetric flow rate of species A fed at the first reactor of the series).

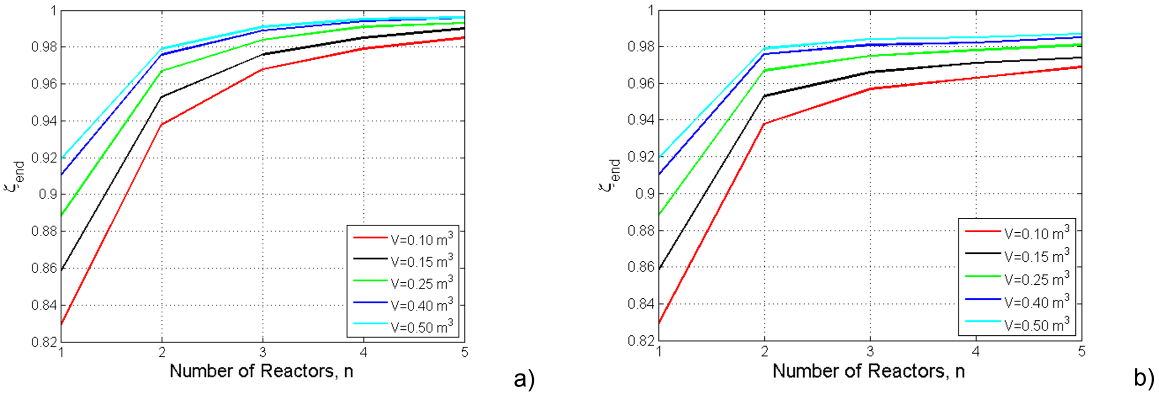
4. Results and discussion

As said before, the main aim of this work was to determine the optimum number of CSTRs in a series capable of both minimizing the reactors volumes (considered equal for each reactor of the series) and fulfilling the constraints expressed by Eq(2), Eq(3) and Eq(4).

Particularly, referring to the relevant case study of the synthesis of nimesulide, two different dosing policies of the species B (nitric acid) have been considered: 1) B is dosed entirely in the first reactor of the series, the remaining reactors (if present) act as workout (that is, residence volumes); 2) the total flow rate of species B is split and dosed over the first (NR-1) reactors of the series, the last reactor acts as workout.

The results of the analysis (found through a numerical resolution of the system of algebraic equations expressed by Eq(7), n=1 to NR) have been reported in Figure 1.

As it is possible to observe, the dosing policy strongly influenced the behavior of the CSTRs series. Particularly, if dosing policy 2 is considered, the minimum requested conversion at the outlet of the CSTRs series cannot be reached for the values of the number of reactors and volumes here considered: that is, NR ranging from 1 to 5 and *V* ranging from 0.1 to 0.5 m^3. Conversely, for dosing policy 1, the minimum requested conversion at the outlet of the series of CSTRs can be easily reached. This behavior can be explained simply considering that, in the case of a dosing stream split among the reactors of the series, the overall concentration of the reactants along the CSTRs series is lower.



a) b)

Figure 1: Conversion at the outlet of the reactors series as a function of the number of reactors and the volume of each reactor in the series for: a) the case of B dosed entirely in the first reactor of the series; b) the case of B dosed in the first (NR-1) reactors of the series.

Particularly, choosing dosing policy 1 the requested value of the conversion is reached using 4 reactors and a volume of 0.25 m^3 each (or using 3 reactors and a volume of 0.50 m^3 each, solution eliminated by the algorithm because the reactor volume is doubled with respect to the selected solution); choosing dosing policy 2 (split of the B dosed stream), the requested value of the conversion is never reached. The solution found for dosing policy 1 corresponds to a real process intensification because the productivity has been doubled and the reaction volumes have been considerably reduced. Moreover, the constraint expressed by Eq(4) is fulfilled since, for case 1, the maximum conversion in the first reactor is 0.8879 leading to a maximum reactor temperature in adiabatic conditions equal to 114,18 °C which is lower than the MAT value. This means that the process can be operated under safe conditions. Of course, such a value could be too closed to the MAT value therefore a split of the B stream along the reactors of the series can be re-considered but, in this case, the volumes will be considerably higher (about 1/1.5 m^3) and the intensification of the process is strongly sacrificed.

5. Conclusions

In this work, the problem of the intensification of potentially runaway reactions through a change in the reactor type, particularly from a SBR to a series of CSTRs, has been faced considering the relevant case study of the nimesulide synthesis. Results obtained have shown that smaller reactor volumes can be easily obtained: this corresponds to safer processes as the heat removal efficiency is known to be higher as the reactor volume becomes lower. Moreover, it has been demonstrated that the dosing policy of the CSTRs series can significantly influence the performances of the system.

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