

Application of Safety by Design Methodology in Evaluating Process Safety for a Duff Reaction Using Predictive Process Simulators

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ABSTRACT: This work presents a Safety by Design (SbD)-driven approach to the evaluation of process safety and reaction modeling that was effective in obtaining enhanced process knowledge and defining a design space for chemical reaction hazards. The SbD approach is presented for a case study involving the process development of the Duff reaction of phenol derivative with hexamine as a formylation reagent in polyphosphoric acid as a solvent. The starting materials were characterized by a thermal scan, and reactions were explored by different calorimetric methods. The enthalpies of physical and chemical rates of starting materials were determined using an isoperibol reaction calorimeter. The adiabatic calorimeter data provided experimental knowledge of possible side and decomposition reactions. The parameters of these reactions were estimated, which is of significant importance for scaling up the processes. The engineering aspects of the process were explored by process modeling using computer process simulators. On the basis of the proposed reaction mechanism and the combination of the heat and mass transfer and the reaction's thermodynamics and kinetics, the safety risk was described by modeling of the process space through safety parameters (e.g., adiabatic time to maximum rate, maximum temperature, and pressure rise) under practical operating conditions of a plant and its equipment limitations (reactor batch size, time of reagent addition, and/or initial jacket temperature).

■ INTRODUCTION

In order to address the potential consequences of possible runaway and decomposition reactions, it is important to ensure safe operating conditions for processes. European regulations such as the Chemical Agents Directive¹ highlight the need to obtain process safety data in order to complete a compulsory risk assessment with the final output through a HAZOP study. The ultimate aim of such studies is to specify and document a detailed basis of safety for the protection of personnel and plant environment from the consequences of a runaway reaction. The kinetic description of reactions enables a calculation of parameters such as time to maximum rate, which is a conceptual parameter introduced by Gygas² that can be used as a safety margin to define an upper safe temperature limit of a process.

Any manufacturing process has certain safety risks, so it is always necessary to establish the hazards associated with its operation. Flammable gases and vapors are identified in most cases, especially organic solvents such as methanol, ethanol, acetone, etc. An understanding of the chemical reactions and material reactivity is an equally critical element of safe processing. The identification, assessment, and characterization of both intended and, more importantly, unintended exothermic reactions are critical to ensure safe scale-up and operation of a chemical process.³ The research in this field started with the thermal decomposition of acetic anhydride and acetic acid.⁴ Grignard reagents have traditionally been explored because of their exothermic behavior, i.e., the magnesium–iodine exchange reaction.⁵ There are an increasing number of pharmaceutical agents currently under development that are monitored through safety aspects.^{6–9}

Modeling appliances (and process simulators as well) in process development are described in relevant covering topics given by the International Conference on Harmonisation of

Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). There is an endorsed guide for ICH implementations Q8, Q9, Q10, and Q11, which describe a new scientific development approach.¹⁰ It is a concrete and practical implementation of some underlying concepts and principles outlined in the Quality by Design (QbD) initiative.¹¹

The QbD initiative aims to ensure pharmaceutical product quality via scientific process understanding, risk management, strategies to control critical quality attributes (CQAs), and multivariate design space definitions.^{9–17} The QbD process has been described and some of its elements identified.¹⁵ Process parameters such as concentration of starting material, equivalents of reagent, and/or reaction temperature and quality attributes such as purity of the product were identified for each unit operation (reaction, workup, filtration, etc.). QbD is a systemic approach to pharmaceutical development that involves designing and developing manufacturing processes in order to ensure predefined product quality and process robustness in a very systematic way.¹⁰ To date, computer-aided process design and simulation tools have been successfully used in the pharmaceutical industry. A similar approach to process safety that uses the same methodology along with the simulation tools can be considered as Safety by Design (SbD), an integration of safety, quality, and productivity at the same time.

During processing of exothermic chemical reactions, such as the Duff reaction of a phenol derivative with hexamine, it should be emphasized that the hazard comes not only from temperature rise (loss of cooling) but from pressure generation as well. These modes of pressure generation can arise from the desired reaction or side/runaway (product decomposition)

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reactions. Identification of how pressure generation occurs is critically important for used/planned equipment. In interpreting calorimetric data, this paper indicates which parameters can be used directly to propose safety margins for safe application. The basis of safety is the implemented and documented system that should either prevent a process from running out of control or provide engineering solutions to control the consequences of the runaway process. In this paper, the formylation reaction of a phenol derivative was used as the model system.

EXPERIMENTAL SECTION

Formylation of a phenol derivative (Substrate) with hexamine (Reagent) was conducted in 105% polyphosphoric acid (PPA) at 80–90 °C for 3 h in order to obtain the 3-formyl-4-hydroxyphenyl derivative (Product) according to the reaction scheme described in Figure 1. The reaction mixture consisted of 1 molar equiv of Substrate with 1.5 molar equiv of Reagent in a solvent volume of 4 vol/wt of Substrate.

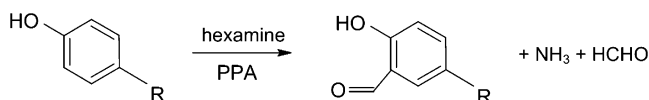


Figure 1. Reaction scheme: the Duff reaction of a phenol derivative with hexamine.

The thermal screening test of the starting material was performed in a differential scanning calorimeter (DSC) (Mettler Toledo) in dynamic mode with an applied heat ramp of 4 °C/min from 30 to 450 °C.

The isoperibol reaction calorimeter (IRC) consisted of a 100 mL thin glass reaction cell immersed in the bath (Julabo). The cell was equipped with a stirrer, a pH electrode, a peristaltic pump, a stabilized voltage calibration heater, and a temperature probe. The cell and bath temperatures and the power on the calibration heater were measured using a National Instruments SCXI-1000 system with a 16 bit A/D converter. Between successive operations the cell was calibrated by being heated with the defined electric heater power.

The basic components of the adiabatic calorimeter, the Advanced Reactive System Screening Tool (ARSST) (Fauske & Associates, LLC), included a 10 mL open spherical glass test cell, a heater, insulation, thermocouple(s), a pressure transducer, and a 350 mL stainless steel containment vessel that served as both the pressure simulator and safety vessel.

The availability of the process simulator DynoChem,²⁵ which can also perform nonlinear parameter regression, significantly removed the restrictions placed by conventional safety analysis and allowed more efficient predictions.

RESULTS AND DISCUSSION

A systematic approach to obtain a better understanding of the hazards of the process is proposed by considering the reactants used in the process, their physical and chemical properties, the process conditions, calorimetric measurements, the equipment used in the process during the development stage, and finally, the scale-up to production scale. It is important to identify any reaction that could generate permanent gases, which could cause overpressurization of a vessel. Even in this early phase of the process development it is possible to identify and solve

Table 1. Heats of decomposition of the compounds involved according to CHETAH calculations¹⁹

compound	ΔH_{dec} (kJ/g)
Substrate	−2.319
Reagent	−3.023
formaldehyde	−4.195
Product	−2.386

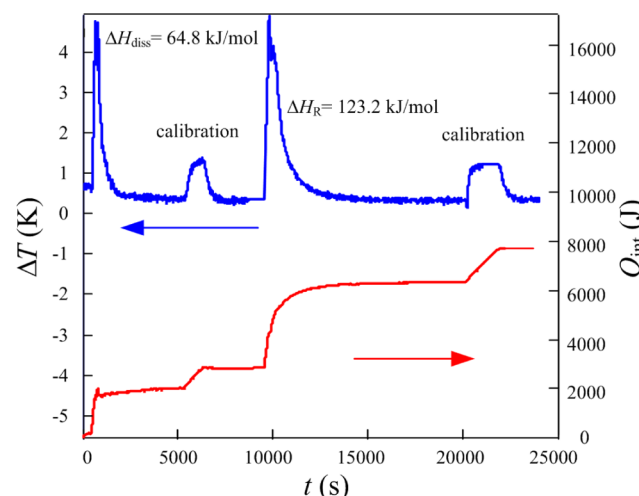


Figure 2. Baseline-corrected temperature difference between the cell and bath (blue) and the integral heat (red) during the Duff reaction of Reagent with Substrate as determined using the IRC.

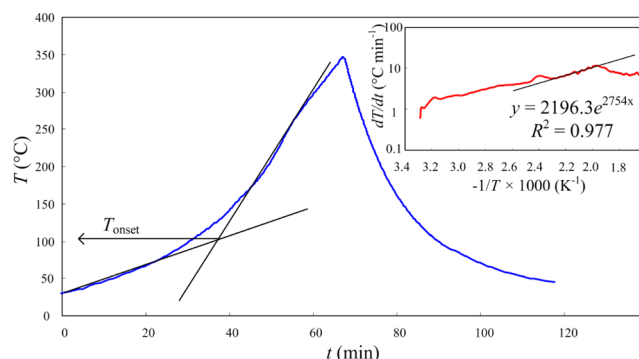


Figure 3. Thermal instability profile of the representative reaction mixture measured using the ARSST and (inset) simple Arrhenius kinetics.

safety problems and, at the same time, positively contribute to the overall optimization of the process.

Functional Group Analysis. Oxygen balance (OB) is an expression that is used to indicate the degree to which an explosive can be oxidized.¹⁸ The product of the monitored reaction, the 3-formyl-4-hydroxyphenyl derivative, has OB > −200 and should be considered as potentially hazardous. According to the reaction scheme, the byproducts of this reaction are ammonia and formaldehyde. Formaldehyde could then be converted to gaseous CO and H₂ and thus could represent a source of pressure rise.

The next step is to calculate the enthalpies. CHETAH¹⁹ is a software package for predicting thermodynamic properties of a reaction and its components. Predictions are accomplished by knowing the molecular structures of the compounds involved in the reaction based on Benson's method of group additivity.²⁰

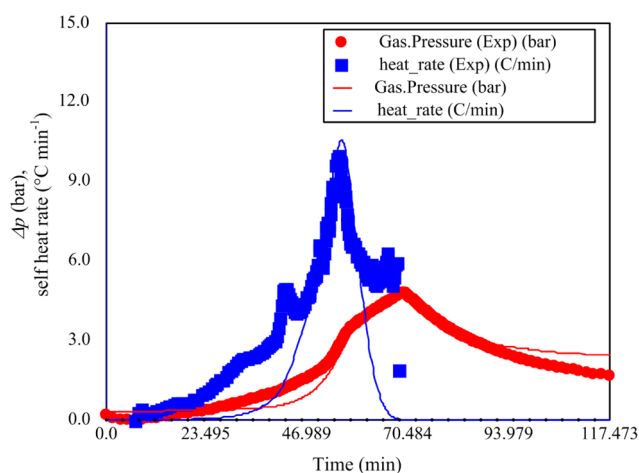


Figure 4. ARSST measurements showing agreement between theoretical and experimental values of pressure and heat rate for runaway reactions.

CHETAH was used to calculate the heats of decomposition for all of the compounds involved (Table 1). Hexamine and formaldehyde have $\Delta H_{\text{dec}} > 2929 \text{ J g}^{-1}$, which is the limit value concerning risk.²¹

Thermal Stability. According to the DSC data for the crude starting materials, exothermic peaks for the Reagent and Product were observed. While the Substrate is stable up to 450 °C, the Reagent (hexamine) has an exothermic peak above 500 J/g (with normalized decomposition enthalpy $\Delta H_{\text{dec}} = 587 \text{ J/g}$) at an exothermic onset temperature (T_{onset}) of 219 °C, which indicates a potential risk, but it does not have groups with limited stability or highly energetic functional groups. The decomposition enthalpy of the Product is below 500 J/g, which is an acceptable level of risk^{20,22} with $T_{\text{onset}} = 277 \text{ °C}$.

Reaction Heat. Determining the heat (enthalpy) of the reaction with the use of the isoperibol reaction calorimeter is based on the application of Tian's equation:²³

$$\dot{Q}(t) = \frac{dQ}{dt} = UA\Delta T + C \frac{dT}{dt} \quad (1)$$

where t is the time, ΔT is the temperature difference between the cell and bath, $\dot{Q}(t)$ is the heat flux, U is the overall heat transfer coefficient, A is the heat transfer area, and C is the heat capacity of the cell and its contents. The heat flux is calculated from the instrumental parameters UA and C (determined by calibration) and the time derivative of the temperature difference. The heat flux curve for a simple reaction has the same shape as the kinetic curve and can be used to estimate the kinetic parameters. The heat of the reaction, $Q(t)$, is calculated by integration of the heat flux.

According to thermal analysis (Figure 2), the addition of the Substrate has an enthalpy of dissolution (ΔH_{diss}) of -64.8 kJ/mol (eq 1). The enthalpy of the reaction between the Substrate and the Reagent is $\Delta H_r = -123.2 \text{ kJ/mol}$, which corresponds to the maximal adiabatic rise of 37 °C, calculated from the specific heat capacity measured from calibration. The experimental data show a significant reaction heat, indicating a potential risk for this system, so this material should undergo additional analysis. However, as the reaction between reactants proceeds very slowly at low temperatures and becomes faster only at higher temperatures, it is important to characterize the system using an adiabatic calorimeter.

Table 2. Assumed reaction scheme with estimated constants and statistical values

reaction	equation	constant	final value	units	SE	CI (%)	t statistic	prob (%)
desired reaction	Substrate + Reagent → Product + NH ₃ + HCHO	k	2.39×10^{-7}	$\text{L mol}^{-1} \text{s}^{-1}$	3.23×10^{-7}	270.355	0.7398	45.97
		E_A	60.024	kJ/mol	8.14	27.124	7.374	0.001
		ΔH_r	-123.229	kJ/mol	1.44×10^5	2.33×10^5	8.57×10^{-4}	99.93
gas formation	HCHO → CO + H ₂	k	1.00×10^{-4}	s^{-1}	0.1363	2.73×10^5	7.34×10^{-4}	99.94
		E_A	81.967	kJ/mol	1.95×10^4	4.77×10^4	0.0042	99.67
		ΔH_r	-183.508	kJ/mol	1.44×10^5	1.57×10^5	0.0013	99.90
decomposition	Product → decomposition products	k	1.87×10^{-9}	s^{-1}	2.90×10^{-7}	3.10×10^4	0.0064	99.49
		E_A	134.379	kJ/mol	54.968	81.811	2.445	1.48
		ΔH_r	-185.088	kJ/mol	3.72×10^3	4.02×10^3	0.0497	96.04

Table 3. Initial values for runaway predictions on all monitored scales

process	T (°C)	V_{liq} (L)	UA (W K ⁻¹)	$UA(v)$ (W L ⁻¹ K ⁻¹)	m_{PPA} (kg)	m_{Reagent} (kg)	$m_{\text{Substrate}}$ (kg)	V_{gas} (L)	p (bar)
IRC	80	0.100	—	—	0.456	0.048	0.060	—	1.013
ARSST	30	0.010	0	0	0.0125	0.0013	0.0016	0.232	30.0
pilot	85	22	60.097	0.5237	41.8	4.4	5.5	113	1.013
production	85	956	114.58	0.3392	1482	156	195	1097	1.013

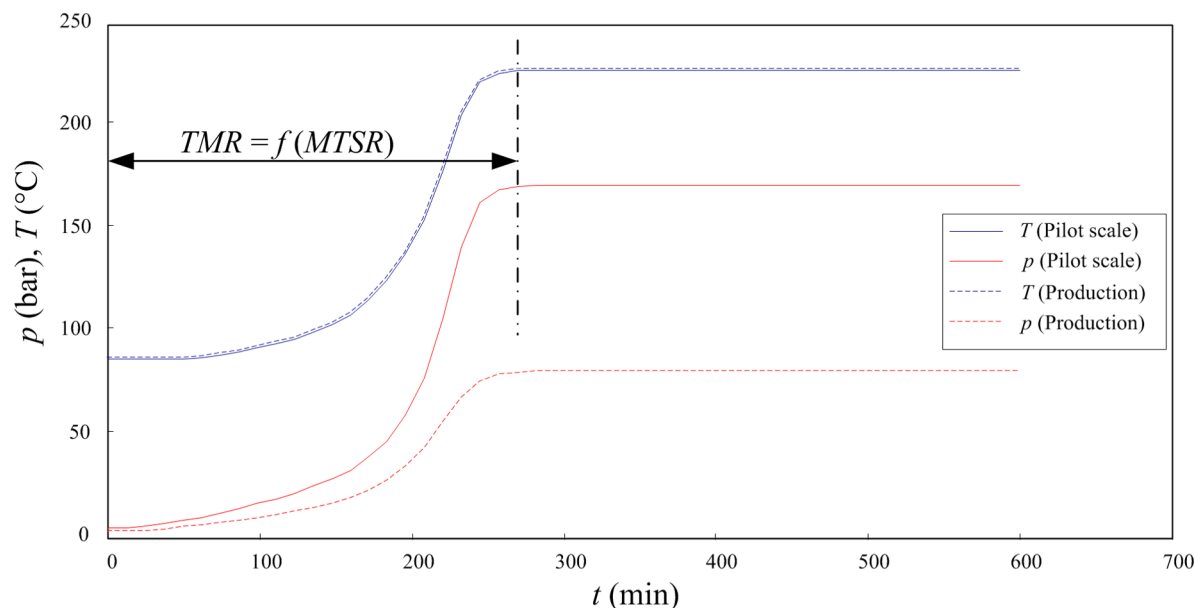


Figure 5. Simulation of a runaway reaction for (a) pilot scale (solid lines) and (b) production scale (dashed lines).

Adiabatic Temperature Rise. The temperature rise for runaway and decomposition reactions is measured. All of the heat generated from the reactions goes into heating the sample (ARSST thermal inertia factor (ϕ) = 1.06). The standard enthalpy of reaction, ΔH_{rxn} , is the enthalpy change that occurs in a system when 1 kilogram (or mole) of matter is transformed by a chemical reaction under standard conditions:

$$\Delta H_{\text{rxn}} = C_v \Delta T_{\text{ad}} \quad (2)$$

where ΔH_{rxn} is the heat of the reaction (in kJ/kg) and C_v ($\approx C_p$) is the average heat capacity of the sample (in kJ kg⁻¹ °C⁻¹).

A representative reaction mixture (see Table 3) was charged into the adiabatic calorimeter (ARSST). The system was pressurized to 30 bar, and then the heating ramp of 2 °C/min was applied up to the temperature of decomposition (350 °C). The adiabatic temperature rise for the monitored system was $\Delta T_{\text{ad}} = 159.09$ °C. The heat capacity (specific heat) of phosphoric acid is $C_p = 1.217$ kJ kg⁻¹ °C⁻¹ (PPA 100, above 100 °C).²⁴ The heat of reaction is $\Delta H_{\text{rxn}} = 193.61$ kJ/kg.

Simplified Arrhenius kinetics (shown in the Figure 3 inset) provides an equation for how the rate of reaction of substance A (r_A) varies with temperature:

$$r_A = -\frac{dc_A}{dt} = kc_A^n \quad \text{where} \quad k = Ae^{-E_A/RT} \quad (3)$$

in which k is the rate constant (in s⁻¹), A is the pre-exponential factor (in s⁻¹), E_A is the activation energy (J/mol), R is the universal gas constant (in J mol⁻¹ K⁻¹), and T is the absolute temperature (in K). It is recommended to reduce the data with the self-heating rate, so the value of the activation energy obtained from eq 3 is $E_A = 22.9$ kJ/mol, and the pre-

exponential factor is $A = 2.196 \times 10^3$ s⁻¹. These values can be used as the initial point for nonlinear fitting.

Adiabatic Pressure Rise. The sources of pressure increase are vapor pressure, gases formed during the desired reaction, and gases formed at elevated temperatures above the normal operating range (affects relief system design). From the measured pressure difference Δp at room temperature (Figure 4) and the ideal gas law, the number of moles of noncondensable gas (n) is given by

$$\Delta pV = nRT \Rightarrow n = \frac{\Delta pV}{RT} \quad (4)$$

where V is the void volume for the test. The measured amount of generated noncondensable gas was $n = 0.0215$ mol (eq 4). The reaction mixture produced 0.0215 mol of noncondensable gas, which corresponds to 0.00140 mol per gram of the reaction mixture. This value can be used to calculate the pressure rise upon scale-up according to the ideal gas law.

Mathematical Model of the Decomposition Reaction. In order to develop a mathematic model, it is necessary to understand the reaction mechanism. The assumptions are that all of the reactions are in the bulk liquid phase with reaction scheme shown in Table 2, represented by equations. The reaction parameters, namely, the activation energies (E_A), reaction enthalpies (ΔH_r), and reaction rate constants (k), are estimated from reaction calorimetry experiments (ARSST). These parameters are of significant importance in scaling-up processes and can be used for transient prediction in cases where different equipment is used and different scenarios are assumed (DynoChem predictions).

The experimental data were analyzed by simultaneous numerical methods for solving partial differential equations

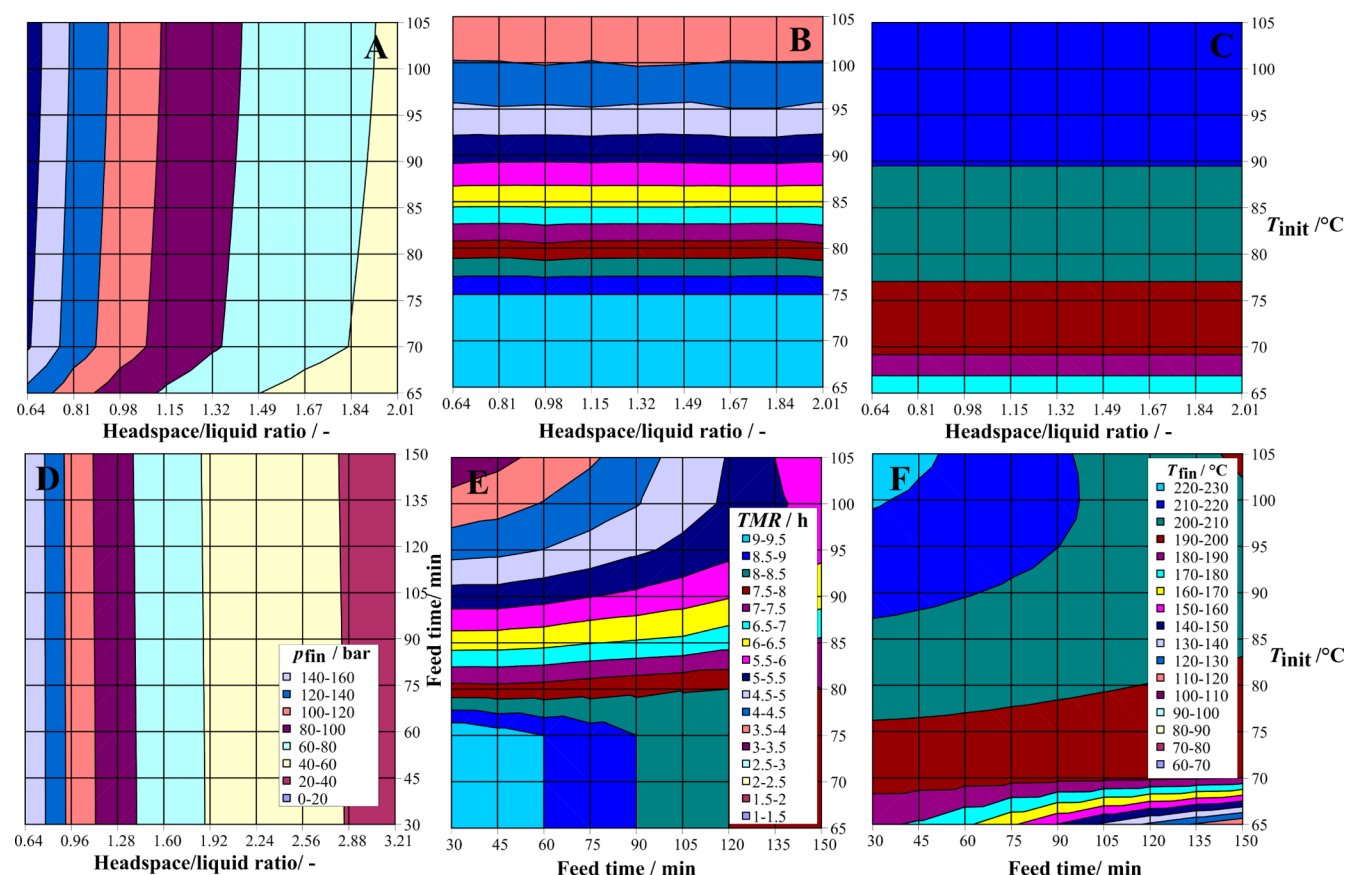


Figure 6. Two-dimensional contour plots of the response surface after 10 h of reaction: (A) p_{fin} vs headspace/liquid ratio and T_{init} at $t_{feed} = 60$ min; (B) TMR vs headspace/liquid ratio and T_{init} at $t_{feed} = 60$ min; (C) T_{fin} vs headspace/liquid ratio and T_{init} at $t_{feed} = 60$ min; (D) p_{fin} vs headspace/liquid ratio and t_{feed} at $T_{init} = 85$ °C; (E) TMR vs t_{feed} and T_{init} at headspace/liquid ratio = 1.41; (F) T_{fin} vs t_{feed} and T_{init} at headspace/liquid ratio = 1.41.

with the Rosenbrock method and simultaneous evaluation of model parameters by the Levenberg–Marquardt algorithm using the DynoChem software package. As the initial values, the constants from the previous analysis were used, which were obtained from linear fits and from IRC estimation. Each estimated constant with the standard error of the fit (SE) can be seen in Table 2. The confidence interval (CI) is expressed as a percentage of the parameter value. In general, for some values the confidence interval is greater than 100%, which means that the fit is unreliable (statistically insignificant). We are confident in using these values because they were used in previous experiments (HPLC vs time for the desired reaction for the estimation of k and E_A) and have similar values (CHETAH, DSC, and IRC).

TMR Calculations. The mathematical model reveals a number of pieces of information, such as consequences of a cooling failure, consequences of pressure release system (burst disc) failure, and time left for countermeasures after the cooling failure.

The kinetic description of the reactions allows a rigorous calculation of the time to maximum rate (TMR) without the need to define the maximum temperature of the synthesis reaction (MTSR).² Gyax assumed in his TMR definition that the time to reach the MTSR could be neglected and focused on showing that $TMR = f(MTSR)$.

Dynamic simulations of reactions in the case of adiabatic decomposition at the end of reagent dosing (at $t = 0$; $UA = 0$ W/K) were performed for different laboratory scales (100 and

10 mL), pilot scale (100 L, Pfaudler), and production scale (2000 L, Lampart) (Table 3). The heat transfer properties of the larger reactors were estimated from step response measurements with water contained in the reactor vessel:

$$UA_{tot} = UA + UA(v) \cdot V \quad (5)$$

With the use of kinetic models of the desired reaction along with side/decomposition reactions, the concept of MTSR is no longer required. In many cases, TMR calculations assume that the worst time for the loss of cooling capacity is at the end of the dosing, as is the case in this model. In our case where the desired reaction is kinetically coupled with the decomposition (Figure 5), i.e., on the way to operating temperatures where there is already a significant contribution of the decomposition reaction, the TMR can be significantly shorter, and this needs to be considered when using this concept of TMR as a quantitative measure of thermal risk. The pressure increase also depends on reactor compliance, with the assumption of a sealed reactor. In this case, for the calculation of the pressure increase, gases released during side/decomposition reactions are included in the calculation for relief system design considerations.

Design Space. In order to determine the desired operating conditions with the hazard considerations during the scale-up process, mass balance and equipment must be considered to provide a robust process with realistic and practical plant operating conditions. In order to simplify the representation of the design space, we decided to specify the maximum allowed

levels for the scale-up process. The reaction temperature (T_{init}), the feed time (t_{feed}), and the reactor compliance (batch size), defined as the headspace (gas)/liquid ratio, were used as the main inlet parameters for response surface analysis. The final temperature (T_{fin}), the TMR, and the pressure increase (p_{fin}) as responses were considered according to the scale-up simulation (Figure 6).

According to the scale-up simulation to production scale (Figure 6) for the explored Duff reaction performed for 10 h at 85 °C with $t_{\text{feed}} = 60$ min at a headspace/bulk liquid ratio of 1.41:1, the adiabatic TMR is 6.35 h with a temperature rise to $T_{\text{fin}} = 206.61$ °C ($\Delta T_{\text{ad}} = 121.61$ °C) with a pressure increase of $\Delta p = 79$ bar. Since the pressure increase is a function of the gas space volume, the prediction of the pressure increase can be represented with response surface analysis (Figure 6), from which it can be concluded that the feed time does not affect the pressure rise (Figure 6D) but the headspace/bulk liquid ratio does have a significant effect (Figure 6A). The TMR is strongly affected by the feeding time and initial temperature (Figure 6E) but not by the headspace/bulk liquid ratio (Figure 6B). The final temperature after 10 h is strongly influenced by the feeding rate and initial temperature (Figure 6F).

CONCLUSION

Process scale-up is characterized by a high level of parameter variability, and adequate thermochemical data must be accumulated during the development. A strategy is required to review the existing chemical and thermal stability data and apply this knowledge to the specific processing environment of the pilot and production plant.

When the model reaction mixture was scanned in an adiabatic calorimeter with the use of a 2 °C/min temperature ramp, exothermic decomposition with an adiabatic temperature rise of $\Delta T_{\text{ad}} = 159.09$ °C and significant gas generation (0.00140 mol per gram of the reaction mixture) was observed. The system temperature rapidly rose to 350 °C at a peak rate of $dT/dt_{\text{max}} = 11.50$ °C/min. While the onset temperature, $T_{\text{onset}} = 161$ °C, is generally above the typical operating temperature for these reactions, it is nonetheless important to cautiously evaluate the process for analogous decomposition events in case of cooling failure (at the end of reagent dosing).

This evaluation was accomplished using response surface methodology by modeling the process through operational parameter space. This combination of conditions implies that deviations are not uncommon, and this approach enables understanding and reduction of the high potential risk of runaway reactions. The response surface explores the process and plant, looking for scenarios that may have hazardous consequences.

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Notes

The authors declare no competing financial interest.

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