In the chemical and pharmaceutical industry, most processes are carried out in batch or semi-batch mode. The hazard potential and risk of chemical processes are related to reactivity and toxicity of chemicals involved and the process design itself.

While the toxicity of the reagents cannot be influenced, the appropriate design of a process is essential to keep the reaction under control at any given time. As there is no steady-state in batch and semi-batch operation, the process dynamics becomes an important factor too and needs to be assessed carefully. Consequently, striving for an intrinsically safe process is thus the goal of process development.
1 Thermal Risks in Chemical Production

The risks and hazard potential of chemical processes are affected by a number of different parameters, such as:

- Heat transfer
- Effect of mixing
- Kinetics and heat generation rate
- Overall heat balance
- Heat removal capacity of the reactor
- Accumulation of reagents and energy
- Physical properties and stability of the reagents and the reaction mass

Thermal runaway scenarios in a chemical plant can be ultimately related to conditions in which the heat generation of an ongoing reaction exceeds the heat dissipation capacity of the process equipment. A number of cases can be identified:

1. Generally, during a chemical process the reactor is in an unstable equilibrium state (Figure 1), where the desired reaction releases heat. In case of reactant accumulation and a simultaneous failure of the cooling system, the heat production rate persists and whatever energy potential is present at this moment will be released adiabatically.

2. The predominant hazard in the manufacturing process however, is loss of control of the desired reaction, e.g. due to reactant accumulation, high sensitivity to impurities, problems with initiation (long induction time), wrong kinetic assumptions etc.

3. The energy balance is dominated by a low heat dissipation capacity and subsequent accumulation of energy. In this case, even very weak undesired reactions can run away.

4. Furthermore, undesired operational conditions may lead to insufficient mixing, wrong or too high feed rates, wrong temperatures etc.

5. The runaway of the desired reaction can also be the reason for secondary undesired events. First, it causes an intermediate temperature level to be reached by the runaway of the desired reaction. It is called MTSR (Maximum Temperature of the Synthesis Reaction = maximum achievable temperature based on the amount of accumulated reagent) or MAT (Maximal Attainable Temperature = maximum achievable temperature in the worst case assuming 100% accumulation of reagents). Starting from MTSR, further events, particularly decomposition reactions, can be triggered which may ultimately lead to an explosion.

6. Finally, undesired reactions may occur rapidly if reactive compounds are mixed accidentally, e.g. if cooling water penetrates into the reaction mass

![Figure 1. Heat balance diagram. A typical semi-batch is run at the unstable operating point]
2 Runaway Scenarios

In order to evaluate potential runaway scenarios, data to predict their progress needs to be evaluated including thermodynamic and kinetic analysis of the reacting system. Because it is not feasible to completely model the reaction in practice, the analysis can be reduced to a number of basic properties and relatively easy-to-obtain data. Based on these data, the risk can be presented as a ‘Runaway Graph’ (Figure 2).

The data used in the graph are determined by answering the following questions:
1. What is the heat evolution rate of the process as a function of time \( q_R(t) \) with which the equipment has to cope?
2. What temperature will be reached when the desired process runs away, assuming adiabatic conditions for a cooling failure (MTSR or MAT)?
3. When is MTSR maximal? (most critical instance for a cooling failure)
4. In what time, \( \Delta t_{Dec}(T_0) \), will a runaway decomposition reaction develop, given the initial temperature \( T_0 \) (in this case, \( T_0 \) is typically equal to MTSR)? This time can be either related to the heat production rate at \( T_0 \) by assuming zero order kinetics (Time to Maximum Rate or TMR) or by explicitly integrating isothermally measured heat production rates as a function of time.
5. In what time, \( \Delta t_{R}(T_0) \), will MTSR be reached?
6. What is the order of magnitude of an adiabatic temperature increase \( (\Delta T_{ad, Dec}) \) caused by the runaway of secondary reactions and what are the consequences?

MTSR: Maximum Temperature of the Synthesis Reaction
MAT: Maximum Attainable Temperature
MTT: Maximum Technical Temperature
TMR: Time to Maximum Rate
\( \Delta T_{ad, R} \): Adiabatic temperature increase of desired reaction
\( \Delta T_{ad, Dec} \): Adiabatic temperature increase caused by secondary reaction
\( \Delta T_{Dec} \): Time in which MTSR is reached
\( \Delta t_{Dec} \): Time to runaway at a given temperature
\( q_R(t) \): Heat evolution rate
\( T_r \): Reactor temperature
\( T_j \): Jacket temperature
\( T_p \): Process temperature
\( T_{D24} \): Temperature at which TMR is 24h
3 Data Requirements

From the previous questions it becomes evident that data related to the energy potential of the reaction mass as well as data related to the reactant accumulation and heat evolution characteristics need to be determined.

The most appropriate tool to obtain information of the desired reaction is the Reaction Calorimeter RC1e® which allows a chemical reaction to be run under conditions representative of a specific process. The measurement of the heat flow serves as a direct indicator of the reaction rate and provides the basic data required \[ q_R(t), \Delta T_{(T_p)} \].

The accumulation of reactants during the process is calculated from the addition and the conversion as a function of time. The accumulation of energy is obtained by the integration of the heat flow curve, from which \( \Delta T_{\text{act}} \), MTSR and MAT can be derived.

The energy potential of the reaction mass can be determined by micro-thermal analysis (e.g. Differential Scanning Calorimetry, DSC), where typically the mixture of the starting materials and samples from intermediate process phases are investigated. A comparative evaluation of the results indicates which signals correspond to the desired and undesired reactions.

The data of the heat evolution dynamics of secondary reactions can be obtained from either isothermally or dynamically measured heat evolution rates, typically using DSC techniques or adiabatic calorimetry, e.g. ARC. Adiabatic experimental techniques require a careful selection of the experimental regime and are less adequate for modeling reactions with complex kinetics.

Apart from these basic data, physical properties such as boiling points, heats of vaporization, vapor pressures, etc. and data related to process equipment are used to assess the consequences of a thermal runaway.
4 Evaluating the Risk and Criticality of a Process

The risk of a process depends on the severity and probability of its occurrence. The criticality of the runaway can thus be evaluated using the relative levels of the different temperatures attained if the desired reaction and the decomposition reaction proceed under adiabatic conditions.

The probability can be estimated using the time scale. If there is enough time left to take emergency measures before the runaway becomes too fast after the cooling failure, the probability of the runaway will remain low.

The criticality of a reaction presenting a thermal potential overall can be estimated by looking at the following four temperatures:
- \( T_p \) (process temperature)
- \( MTSR \) (Maximum Temperature of the Synthesis Reaction)
- \( TD24 \) (temperature at which the Time-to-Maximum-Rate (TMR) is 24 hours)
- \( MTT \) (Maximum Technical Temperature, e.g. boiling point, maximum allowed pressure, material, etc)

The graphical representation of these temperature levels (Figure 4) allows the classification of a process from non-critical to highly critical. Depending on the allocated criticality class a process might be safe and not require any modifications at all. However, it also may require slight or considerable modifications, or a complete re-work of the entire process.

**Figure 4.** Criticality Graph from iCSafety™ software
5 Striving for Intrinsic Safety

Design Safe Processes

In process development normal operating conditions are assumed. However, when developing a safe process, deviations from the normal operating conditions must be considered by asking questions like "What happens if...?"

The integration of risk analysis into process design at an early stage of the development provides the opportunity to design an inherently safe process. Used correctly, risk analysis becomes an iterative procedure accompanying the process development.

The rules for improving process safety by an appropriate design are almost trivial:

- Know your chemistry: Are there dangerous side reactions? Which conditions favor them? Which parameters may have an influence on the reaction rates of the main reaction? Can initiation be a problem?
- Avoid unnecessary accumulation of exothermally reacting compounds
- Maximize heat transfer capacities per unit of reactor volume
- Avoid external sources which trigger runaways

As mentioned earlier, most of the processes in the chemical and pharmaceutical industry are run in batch or semi-batch mode.

The batch-mode however, is strictly acceptable for non-hazardous reactions only (moderate $\Delta T_{ad}$, no exothermic decompositions at the MTSR). If these conditions are met, batch or adiabatic batch reactions are a safe and cost effective way of operation. If they are not met, running the process in semi-batch operation, where the addition of one or more of the reactants is controlled, is preferred.

Typical heat accumulation problems occur if the heat producing effects and the heat dissipation rate are not in equilibrium, e.g. the heat production is larger than heat removal even if the heat production is only very small. This may particularly be the case in highly viscous liquids or reaction masses with high solid contents.

In case of fast or very fast reactions, continuous operation (flow or plug flow reactors) is the most effective way to run a process. This is of particular importance for the production of thermally unstable products (e.g. explosives), but also has its limitations.

Even though chemical manufacturing should be intrinsically safe, classical defensive safety measures must not be abandoned or neglected. Emergency control, such as emergency and evaporation cooling, quenching, dumping, controlled depressurization or pressure relief will remain an important function of the process control systems or even a regulatory requirement.
6 Study of a Semi-Batch Nitration Reaction

The following experiment describes a nitration reaction run in sulfuric acid. The traditional process was run in the semi-batch mode where mixed acid (with a 67% excess) is added continuously at 80°C isothermally to an aromatic substrate dissolved in sulfuric acid over a ten hour period.

The process presents various difficulties with respect to thermal process safety:
• The reaction is rather slow. Therefore, a continuous reactor is not the preferred solution as the mean residence times would be unrealistically long.
• A highly exothermic decomposition reaction is able to take place very slightly above the process temperature
• The solvent does not provide any capacity for evaporation cooling

Based on this example, the thermal hazards assessment procedure and the development of an optimal semi-batch process are explained.

6.1 Information from Differential Scanning Calorimetry (DSC)

At first, the mixture of starting materials was investigated by DSC showing the slow behavior of the desired reaction (blue curve, Figure 5). Looking at the energy potential, an adiabatic temperature increase of 135K is calculated which results in a maximum temperature of the desired reaction (MAT) of 215°C.

However, the reaction mixture also shows a highly exothermic decomposition above 200°C which is a concern for two reasons (green curve, Figure 5):

a. If a cooling failure occurs once the full amount of reagent is added the adiabatic reaction would increase the process temperature to a maximum of 215°C (MAT) which is beyond the onset temperature of the highly exothermal decomposition reaction

b. With an onset temperature of about 200°C it can be assumed that the decomposition reaction has already initiated while the desired reaction is ending. In order to estimate runaway times as a function of initial temperatures, further analysis and additional quantitative data on the runaway dynamics of the decomposition reaction are required.

Sample size: 10-20mg
Heating rate: 4°C/min

<table>
<thead>
<tr>
<th>Results</th>
<th>Derived Data (Adiabatic temperature increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat of desired reaction: -175kJ/kg</td>
<td>Desired reaction: 135°C</td>
</tr>
<tr>
<td>Heat of decomposition:  -1300kJ/kg</td>
<td>Decomposition reaction: 1000°C</td>
</tr>
<tr>
<td>cp: 1500kJ/kgK</td>
<td>(corrected for equimolar mass)</td>
</tr>
</tbody>
</table>

Figure 5. Micro-Thermal Analysis (DSC) of reactant mixture of an example reaction
6.2 Runaway Dynamics

For simplicity reasons data of the dynamics of runaway reactions are acquired by means of isothermal DSC runs. These are more adequate than those obtained by attempting to simulate adiabatic conditions. In Figure 6 a series of isothermal experiments of the final reaction mixture are shown representing the behavior at different temperatures.

The heat evolution signals as a function of time show an increasing trend with time passing through two maxima.

The maximum heat evolutions as a function of the set temperatures of the isothermal experiments follow the Arrhenius Law in an astonishingly simple manner (Figure 7).

Even though this formally autocatalytic behavior is not mechanistically clear, it can be used to model adiabatic runaway curves (TMR at respective temperature, Figure 8). Subsequently, the runaway times of the decomposition reaction at various temperatures can be estimated.

Based on these results and supposing a runaway time of around 10 to 20 hours is accepted, MTSR must be limited to less than 120°C (often a time of 24 hours is assumed also called TD24).
6.3 Dynamics of the Desired Reaction

As the process temperature is 80°C and the maximum tolerable temperature of the synthesis reaction is below 120°C, we can only tolerate a maximum energy potential equivalent to 40K to be accumulated at any time. This corresponds to a fraction of about 30% of accumulated reactant.

In order to find the actual degree of accumulation, investigations using the Reaction Calorimeter RC1e were run (Figure 9).

Curve A is the heat evolution obtained when running the reaction according to the original process in the reaction calorimeter. A balance between input and output of reactive potential – measured in units of energy – is calculated next, where:

- Curve C is proportional to the actual feed and corresponds to the overall heat of reaction (input)
- Curve B is the integration of the experimental curve A and represents the conversion (output)
- Curve D is the difference between the input (C) and the output (B) and thus, represents the accumulation as a function of time

To obtain MTSR(t) it simply must be divided by the heat capacity (Figure 10).

From the calculations explained above and the trends in Figure 10 (left), it is clear that the reactant accumulation is higher than 50%. As a consequence MTSR becomes 155°C which is clearly above the maximum tolerable.

It is evident, that an adiabatic cooling failure in the moment of equimolar feed would give rise to a runaway of the desired reaction, immediately followed by a runaway decomposition.

Responses to cooling failures occurring at different times in the process have been calculated from the model. Figure 10 (right) confirms that if a cooling failure occurs at a time of around six hours, the temperature rapidly increases due to the nitration reaction. As the temperature is above the limit of 120°C it is followed by a runaway due to decomposition leading to a thermal explosion with severe consequences.

In this domain the process has a «built-in» potential for a catastrophic runaway where safety uniquely depends on the reliability of the cooling system. It is obvious, that the primary cause of such an incident is the loss of control of the desired reaction. The high severity, however, is mainly due to the high decomposition energy.
7 Developing Safer Processes

The process described is far from intrinsically safe and the question arises: How could it be improved?

Apart from more basic procedure changes, such as changing reaction media, reversing the additions, etc., the systematic variation of concentrations, temperature and feed profiles can give rise to a large number of different processes with distinctly different hazard potentials.

An overview for the MTSR’s based on the variation of the temperature and feed time is shown in Figure 11.

While the MTSR seems to be optimal at a process temperature of around 110°C and an increasing feed time, the goal of an MTSR of not more than 120°C cannot be met. On the other hand, the MTSR curve in Figure 12 shows a distinct maximum. Therefore, the problem of MTSR being too high can be bypassed by choosing a variable feed rate. Figure 13 shows a feed profile adjusted so that the MTSR of 120°C is never exceeded.

The process now consists of three different stages:
- In the first stage, the reactant is added as fast as the cooling capacity allows until the acceptable MTSR-value is reached
- The second stage involves decreasing the feed rate to a level maintaining the MTSR-value
- Towards the end of the process the MTSR-value drops and any excess of reactant can be added quickly
8 Conclusions

Crucial for the development of a safe manufacturing process is the availability of information describing the process, the toxicity and stability of the individual raw materials, intermediates and final products.

Careful examination of the process with respect to accumulation, the maximum attainable temperature in the reactor, and possible decomposition reactions are very important. The analysis of the dynamics of the reaction, as well as the subsequent decomposition reaction may allow scientists to model runaway scenarios and establish the ideal reaction procedure. One of the key components in the risk assessment of the example was the availability of kinetics data and reliable MTSR information. The knowledge gained was used to make predictions about the temperature profiles, maximum operating temperature, concentration, and feed rate or feed profiles.

In the example discussed, the proposed process parameters were applied to experiments in the reaction calorimeter, which resulted in a nitration process allowing to manufacture the product with an acceptable risk.

With the RC1e® Reaction calorimeter (Figure 14), iControl™ and iC Safety™ software (Figure 15) and the Differential Scanning Calorimeter DSC 1, METTLER TOLEDO provides the toolbox to support comprehensive process safety studies.
Sources and References


Additional Resources

Webinars
- Francis Stoessel: Avoiding Incidents at Scale-up: Is Your Process Resistant Towards Maloperation?
- Stephen Rowe: Safe Scale-up of Chemical Processes: Holistic Strategies Supported by Modern Tools
- Kevin Drost: Safe Process Scale-up with iC Safety™ - A Case Study of Nitroalkane Chemistry by WeylChem

To watch the webinars, please visit: www.mt.com/process-safety

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