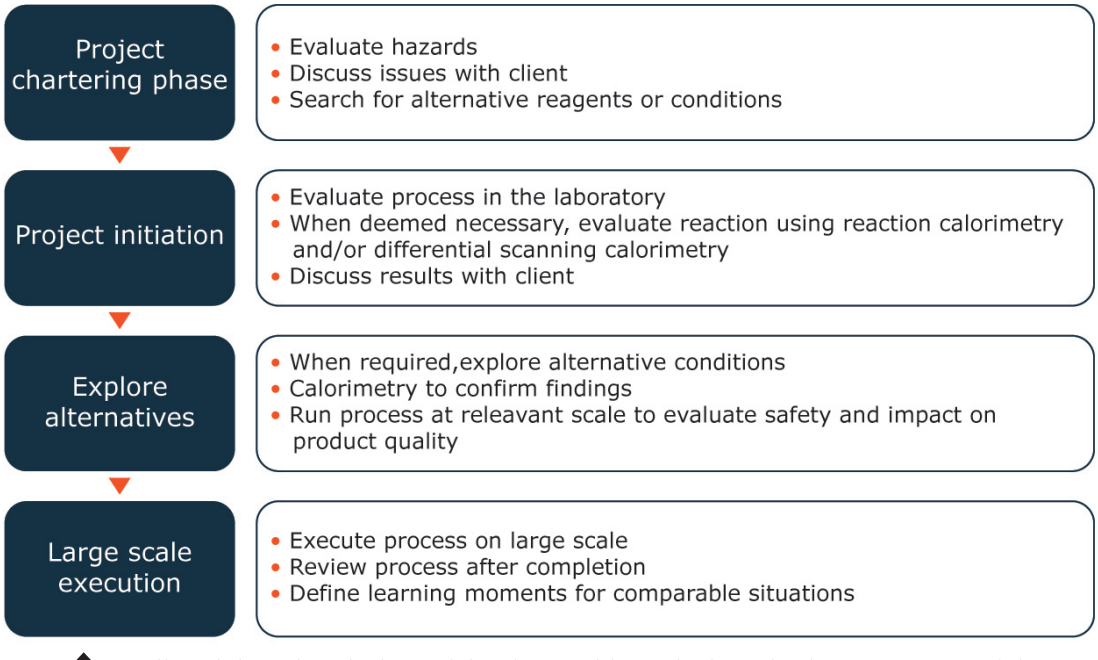
Ardena Insight

Enhancing Safety in Drug Substance Synthesis: A Smart Approach to Chemical Design

Scaling up the synthesis process of new chemical entities may sometimes require the use of hazardous reaction conditions or reagents. It is essential to develop a thorough understanding of the chemistry involved to prevent unsafe situations. At Ardena, we design synthesis processes that are intrinsically safe. During the proposal preparation process, we identify hazardous chemical transformations, reagents and reaction conditions. We inform our customer on potential safety issues and propose alternative reaction conditions and/or reagents during the project chartering phase. During process development, all chemical reactions are thoroughly assessed for hazards.

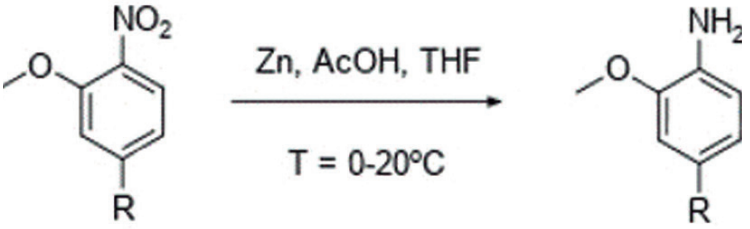
Many accidents in chemical plants are caused by poorly controlled heat-releasing (exothermic) reactions and/or pressure build-up. It is therefore critical to know the energy content of each reaction and to develop chemical processes in such a way that exothermic reactions are controllable or dose-controlled and thus stoppable at any point during processing. Our internal governance at Ardena ensures that such exothermic events are properly assessed via tools such as reaction calorimetry and differential scanning calorimetry. Reaction calorimetry is a well-established technique to determine the thermal profile of a reaction and its associated heat of reaction and (adiabatic) temperature rise. Differential scanning calorimetry analysis is used to identify the onset temperature of hazardous events.



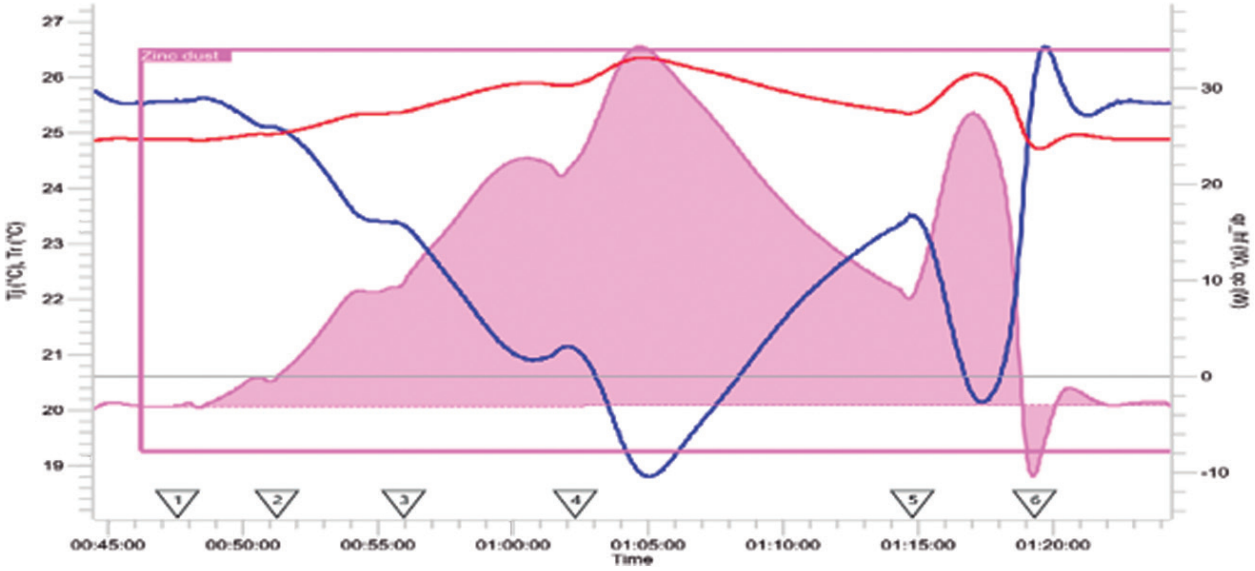
Actions taken at each stage of development to evaluate and enhance process safety.

After establishing safe chemistry, processes are subjected to a demonstration phase and a gradual increase in manufacturing scale, to assess how the chemistry behaves during scale-up and whether the quality of the product is impacted.

The below case of a zinc acetic acid mediated reduction of a nitrobenzene derivative illustrates our safety-by-design approach. Nitro compounds pose a well-known risk in organic synthesis. Reduction of nitro-functionalities is a common reaction in heterocyclic drug substance manufacturing and is usually accomplished using metallic zinc and acetic acid or hydrogenation using a palladium catalyst. In this particular case, hydrogenation was not possible due to the nature of the functional groups present in the substrate molecule. The procedure using metallic zinc and acetic acid was therefore selected and tested on 2-gram scale. According to the initial procedure, metallic zinc was added to the nitrobenzene derivative in THF/AcOH at 0°C after which the reaction mixture was heated up gradually. At 15°C, the reaction started and showed a sharp exotherm with an associated temperature increase to 38°C. Executing the reaction this way resulted in accumulation of reagents and rapid release of heat. At 2-gram scale, the heat release was still readily controllable, but it could have presented a significant hazard at larger scale.



To ensure safe processing, our chemists proposed alternative conditions for this step. The working hypothesis here was that portion-wise addition of zinc at elevated temperature would enable better control over the temperature rise associated with the heat released during the reaction. An experiment in the reaction calorimeter was set up to test this hypothesis (see figure below).



Metallic zinc was added in six portions (each addition is depicted by a triangle on the X-axis) at 25°C. The energy release was instantaneous (pink surface) and by applying cooling (blue line) the reaction temperature (red line) was maintained at 25-26°C. This approach enabled full control over this highly exothermic reaction and was successfully applied at 20-litre scale in our plant.

In summary, risks during chemical processing may be mitigated by:

- Calculation of the reactor's cooling capacity to ensure sufficient capacity is available to absorb reaction heat.
- Ensure that a reaction is dose-controlled, for example by:
  - Addition of reactive reagents at elevated temperature.

    This ensures that dosed reagents are immediately consumed and prevents accumulation.
  - Portion-wise addition of reagents to prevent accidental all-in-one dosing.
  - Reversed addition of reactive reagents.
- Replacing a reaction solvent by a solvent with higher boiling point or higher heat capacity to increase the heat sink.
- Replacing reagents by safer alternatives.