

## Safe operation of highly exothermic reactions in versatile flow reactors

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In the pharmaceutical industry the Early Phase Development of drug substances is typically accompanied by time pressure and the absolute need for reliable supplies of intermediates and final drug substances in regards to quantity and quality. At the same time the attrition rate of potential drug substances is relatively high in this phase, so that front-loading of large work packages is at risk. Consequently, a process is highly attractive if it allows minimizing the workload for further process development before scale-up and supply for toxicological studies on the one hand, but on the other hand ensures timely and safe delivery of the required quantities. In practice this means, it can be beneficial 1) if chemistry can be used similar to the previous Drug Discovery Phase even if it involves a significant thermal potential, 2) if the process can be designed in an inherent safer way compared to the standard semi-batch mode, and 3) if a part of the scale-up risk can be eliminated as by just increasing the total production time of a continuous process. All three points are valid in case of continuous manufacturing, which has been promoted within Novartis Pharma in the recent years accordingly.

Within the Chemical Development Unit of Novartis the following technical concept was established for flow chemistry across all sub-units in Switzerland and China: in each unit a few specialists well familiar with the concepts and advantages of flow chemistry are available as direct partners for the synthesis chemists and the standard project teams. Each unit has access to the same equipment in order to facilitate easy and fast transfer of knowledge and processes. A global safety concept was developed addressing the specific needs of Early Phase Projects, but also to ensure a common systematic and recognized approach for the process risk assessment – helping different disciplines (synthesis chemist, continuous chemist, chemical engineer, safety lab expert) to talk in “the same language”. This approach is mainly based on dynamic DSC (differential scanning calorimetry) measurements without further kinetic information as the latter is usually not available. Thus several worst-case assumptions (e.g. for reaction order, activation energy) are being made during the thermal safety assessment. (1) In addition, further simplifications might be required which lead to a more conservative outcome. (2) The resulting figures are the maximum temperature of the synthesis reaction (MTSR) and the end temperature after secondary reaction ( $T_{\text{end}}$ ), which can serve as measures for the severity of failure scenarios. Each of both temperatures is coupled with the respective adiabatic time-to-maximum rate ( $\text{TMR}_{\text{ad}}$ ), which can be correlated to the likelihood of the failure scenario. Therewith, the total thermal safety risk can be determined as the product of severity and likelihood of an undesired heat release scenario. If required, consequences like re-defining process conditions, further investigations for deeper process understanding (replacing worst-case assumptions by actual figures), or defining emergency measures in case of failure scenarios can be detailed in order to increase the overall safety. The procedure will be shown on the example of a nitro-rearrangement as highly energetic reaction.

During the Late Phase Development the likelihood of a product to be commercialized has been increased significantly. At the same time the need for a substantial scale-up of flow rates and hence reactor volume is obvious in order to supply quantities of typically 50-150 kg compared to a few kilogram during the Early Phase Development. Thus, more detailed process understanding

including kinetic information is required - especially in case of highly exothermic or energetic reactions - whereas the additional effort becomes more reasonable in regards to project schedule and economical aspects.

In respect to the reactor layout a simple plug-flow reactor is often sufficient on lab scale, but on larger scale more dedicated equipment is typically required regarding heat transfer, pressure drop, and large volume segments for high conversion rates. Consequently, a versatile plug-flow reactor consisting of a series of different sections has to be assembled, firstly balancing required local heat duty over reactor volume, and secondly allowing different temperature zones balancing selectivity and safety of the process against reaction rate and costs for reactor volume at high conversion.

This concept was worked out using a highly exothermic Sonogashira coupling with an adiabatic temperature increase of 170 K, including a Hazard and Operability Study (HAZOP). A method will be presented how to assess the thermal risk of an exothermic reaction in such a versatile reactor in a systematical and clear way. The Semenov approach was applied in order to check the thermal robustness of the process in the various reactor sections under normal operating conditions, to avoid areas of high parametric sensitivity, and to estimate the controllability after failure scenarios as long as process flow and heat transfer were continued. (3) In case of more critical failure scenarios - if adiabatic conditions due to stagnant flow were to be expected - the critical diameter ( $d_{crit}$ ) by Frank-Kamenetskii was used to differentiate between inherently safe and more critical sections. (4) Thus, further work on a more detailed risk assessment and risk management could be focused to the relevant sections. For a more comprehensive understanding, the previously described characteristic numbers of MTSR,  $T_{end}$ , and  $TMR_{ad}$  were calculated for each section.

#### References

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