Safety Testing in Scale-Up

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Chemical processes in the pharmaceutical and fine chemical industries often deal with synthesis of highly complex molecules. In the absence of relevant information regarding the risks (toxicity, flammability, explosivity, corrosivity, chemical reactivity, thermal stability, etc.), however, it is a challenge to scale-up from laboratory to manufacturing.

In addition to the simple increase in the inventory of hazardous materials that are to be handled, there are changes in heat and mass transfer characteristics that may affect the progression of a reaction. Processes that are commonly most hazardous to scale-up are those associated with exothermic reactions (i.e., where heat is liberated during the reaction) and those which generate non-condensable gas.

In most cases, the process that is to be scaled-up will be complete, with a significant amount of existing physical property and thermochemical information pertaining to the thermodynamics and kinetics of the desired reaction (and defined deviations), and to the fire and explosion properties of the process materials. The majority of this information will have been compiled prior to pilot-scale operations. It is critical however, that these same data (and possibly some additional data) are available to enable safe scale-up of the production.

In essence, each process hazard should be mitigated with a defined basis of safety. This should be a definitive safety measure (or collection of safety measures) which, when applied to a process, should either minimize the likelihood of an event occurring to an acceptably low level or, where this is not possible, provide a method for protection of personnel, the equipment and/or environment from the manifestation of the event.

Strategy & Organization

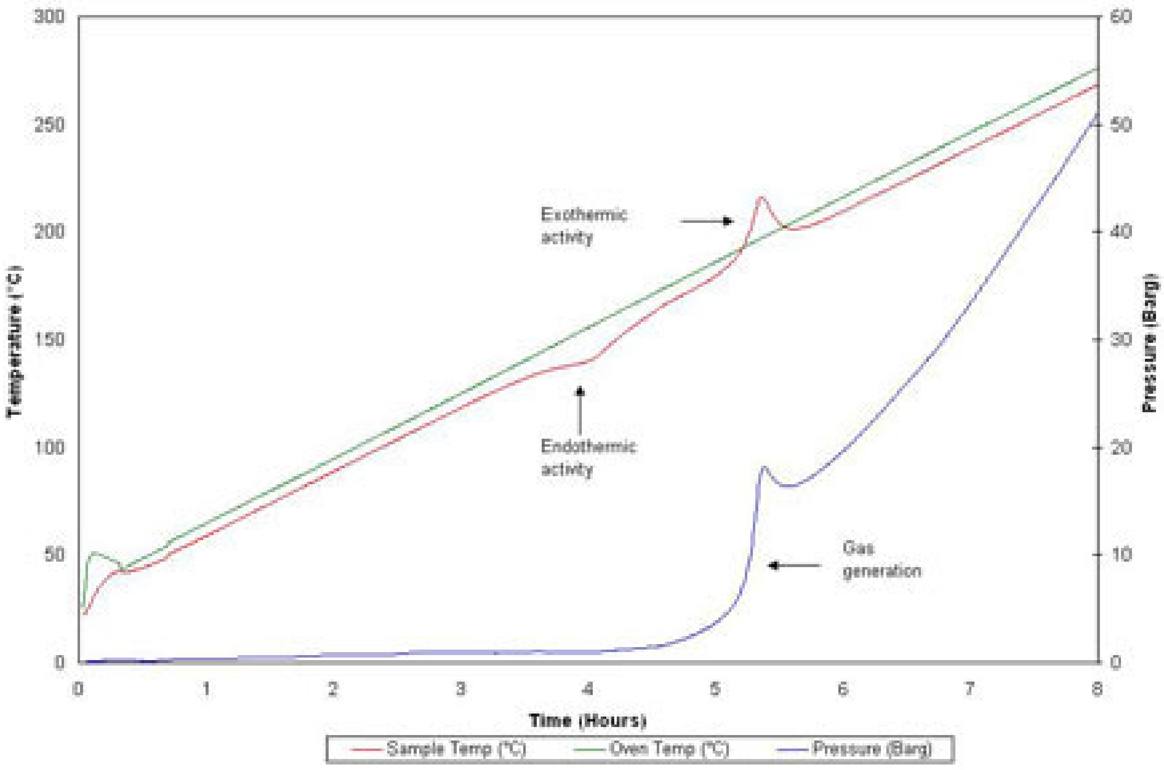
The scale-up of a chemical process will probably be collectively dependent on thorough study by a variety of individual groups within a company. Ideally, a multi-disciplinary team should be appointed to be responsible for each new process to be scaled-up (from laboratory- to full-scale). This team should include personnel from the following departments:

1. Research.
2. Process development.
3. Safety.
4. Engineering.
5. Pilot plant.
6. Production (including possibly a process operator and a mechanic).

7. Analytical.

The attendance of a mid-level to senior manager is desirable, since this individual will be at an appropriate level to influence capital expenditure, and keep track of development costs and timescales. A team leader should be appointed when the team is organized, and the leader would have responsibility for recording and feeding back the team’s findings, and compiling a process technology document (or similar scale-up manual for the process).

The concept of dividing project ownership among the individuals on the scale-up committee can be the most effective method of ensuring a rapid and smooth transition through all of the stages of a process life cycle. The integration of the skill bases of the individuals will also facilitate inter-departmental understanding and cross-fertilization of ideas, concepts and approaches. The same team should be reconvened to consider process developments or modifications, once full-scale production has been realized.



Temperature and pressure traces collected in Carius tube test

Planning

When a process is to be scaled-up, there are usually a number of potential hazards that must be considered via a strategic assessment procedure. With reference only to the thermal hazards posed by a reaction or process, the following issues should be considered:

1. What are the thermal-stability characteristics of the process raw materials?
2. What are the thermodynamics of the desired chemical process and possible undesired reactions?
3. What are the kinetics of the desired chemical process and possible undesired reactions?
4. What are the thermal-stability characteristics of the intermediate process materials?
5. What are the thermal-stability characteristics of the process products and waste materials?
6. Are permanent non-condensable gases evolved at any stage of the process (or during material-handling operations)?

The questions posed above should have been fully considered prior to pilot-scale manufacture.

The organization of safety studies varies significantly from company to company. Ideally, safety should be an integral part of the standard process-development stages. In reality, however, it is usually considered when a process is close to pilot-scale production. The advantage of considering process hazards at a very early stage is that changes to the process can be made to minimize the hazards that are posed without having to re-validate or re-evaluate the process after safety problems have been corrected.

There are a number of critical parameters that must be defined prior to any scale-up operations:

1. What are the safe handling temperatures for the reaction starting materials, and the safe upper (and lower) temperatures for the intermediate and final process streams? Thermal stability trials should be conducted on all isolated process streams to provide information for establishing these parameters.
2. What are the maximum and minimum allowable temperatures to affect the desired chemical conversion? If the temperature is too low, a semi-batch process may suffer from accumulation (i.e., the rate at which material is added becomes significantly greater than the rate at which the material is consumed by reaction). If the temperature is too high, the reaction rate will increase, and the rate of heat evolution may exceed the cooling capability of the reactor jacket and/or coils. In certain circumstances, elevated temperatures may trigger the onset of undesired (side) reactions or decompositions, yielding non-condensable gases. Isothermal reaction calorimetry is usually employed to provide thermodynamic and kinetic data for the desired reaction.
3. What is the rate of gas or vapor generation during the desired process? Gas evolution rate and volume measurements should be incorporated (if necessary) as part of the isothermal process characterization stage. “Tempered” reactions (generating vapors) are more easily controlled than “gassy” reactions (generating non-condensable gases). From the thermal screening tests and isothermal reaction calorimetry, safe operating conditions can be determined.

There are some specific issues relating to scale-up that can cause problems. Generally, these relate to:

1. Changes in the heat-transfer rate, as compared with small-scale equipment (reactor surface-to-volume ratio).
2. Changes in mass transfer (power-to-volume ratio). Agitation is a critical function for safe chemical production since it impacts on the rate at which process materials come together, and the rate at which heat is dissipated from the bulk of the mixture to the vessel wall or internal coils (where heat exchange occurs).

In addition to the factors outlined previously, other effects of scale-up may be equally as critical in ensuring safe manufacture. For example, the following factors should be considered:

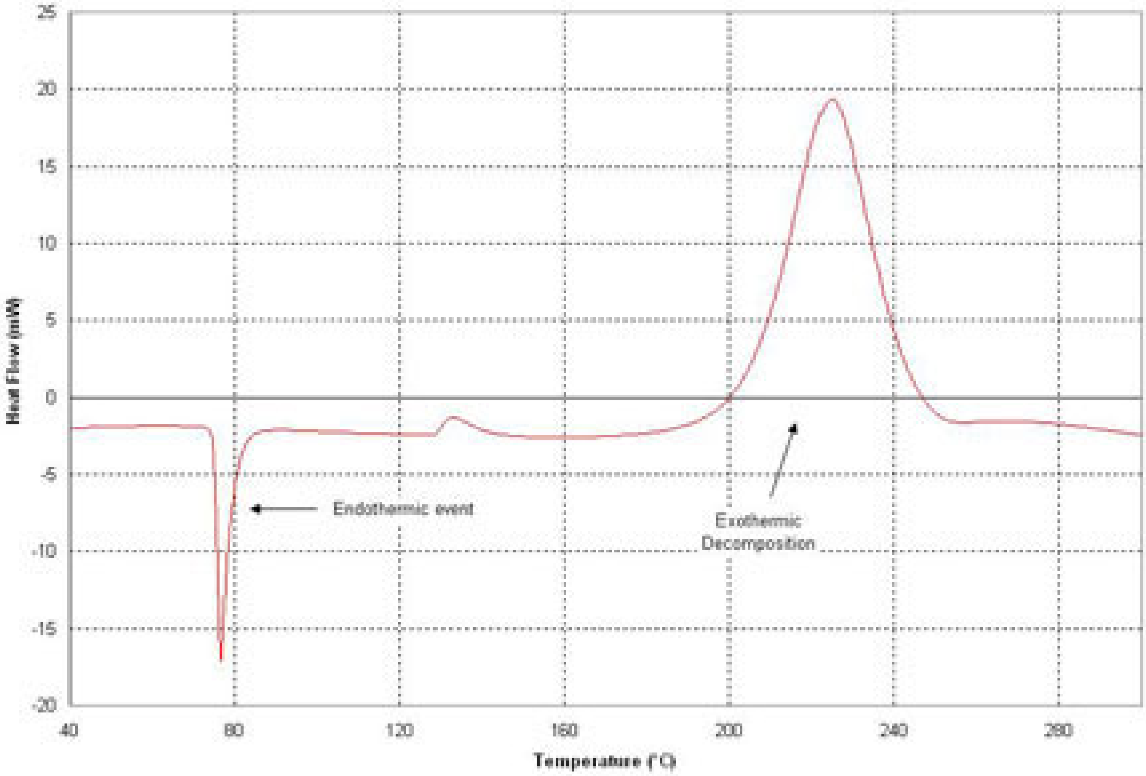
1. Changes in the purity of process materials.
2. Changes in the materials of vessel construction.

Up to this point, the characteristics of the desired reaction only have been considered. In most cases, a process can be conducted safely if the normal procedure is followed. However, the potential for deviations from the normal procedure — as a result of human error or equipment malfunction — must be evaluated. Hazard assessment techniques (such as hazard and operability studies) should be conducted to provide a formal strategy for the identification (and eventual correction) of potential deviations. It is then necessary to ask: What are the consequences of conceivable process deviations on the thermal safety of the process?

The structured hazard-identification approach should be supported by the examination of the consequences of the identified process deviations (either theoretically or, more usually, through further experimentation).

Once the hazard-identification stage has been completed, one or more bases of safety for the production-scale facility should be implemented and documented. Any safety measure that is applied should conform to the appropriate corporate engineering design codes. This applies to process control instrumentation or protective safety measures, such as emergency relief venting, containment systems, etc.

The impact of each basis of safety on the other hazards presented by the process (e.g. flammability, explosibility, toxicity, environmental impact, etc.) must also be rigorously considered.



DSC thermograms, indicating endothermic and exothermic events

Performance Review

The use of a “prescribed” method for assessing scale-up hazards is not considered to be a good approach. In applying such an approach, free thinking is not encouraged and a check-list mentality ensues. By doing this, important issues that may be specific to individual processes may not be considered.

Broad guidelines, which describe the engineering and administrative activities to be conducted, provide latitude for free thinking during the scale-up safety review. At various stages during the scale-up review, adherence of the study to these guidelines should be ensured.

The team as a whole should verify that — at the end of each stage of the scale-up process — the relevant data have been compiled and that there is agreement concerning the elimination or adequate control of safety hazards.

Evaluation of performance should be conducted after startup of each scale-up stage. In cases where unexpected events occur during scale-up, the cause of the event should be identified, and then the scale-up review should be examined to determine the root cause of the deficiency.

Conclusions

Safe scale-up of chemical processes can be achieved in a cost-effective and efficient manner. The utilization of the skills of many different disciplines within the research and development, engineering and production departments, allied to an efficient assessment strategy will achieve this. The selection of the most appropriate experimental technique required to generate the necessary data, combined with its interpretation in the context of the process lifecycle, is pivotal. The approach presented above will achieve safe scale-up in a cost-effective manner with little or no influence on time to market.

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