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JACKETED REACTORS OFFER GREEN SOLUTION

The traditional way to develop a manufacturing process is to do the initial development in round-bottomed laboratory flasks and make the transition to small-scale production-type reactors when the process is ready for piloting; but, suggests Tom Adams, Director Technical Sales, from De Dietrich Process Systems, laboratory-scale jacketed reactors may be an alternative.

The chief advantage of using a jacketed lab reactor is that information is obtained early in development regarding how a process will work in production, including data on its safety. This enables a company to get a drug to market faster and more than justifies the cost of the equipment. GSK, for example, has invested hundreds of thousands of dollars in jacketed lab reactors for its Worldwide Research and Development operations, and Roy Flanagan, team manager of process safety and design with GSK's Chemical Development Department in Research Triangle Park, believes he has saved millions of dollars by getting critical information early in the development of a process. "A blockbuster drug can generate revenues of $1 billion/year — or $3 million/day — so getting products to market faster can have a large and positive effect on the bottom line. In the past, when we used flasks, we had some unpleasant surprises the first time we tested a process in a pilot reactor, and many times we had to go back and redevelop a process. We have had far less of these problems since we adopted the jacketed lab reactors. We typically identify problems early and solve them before we get to the pilot stage."

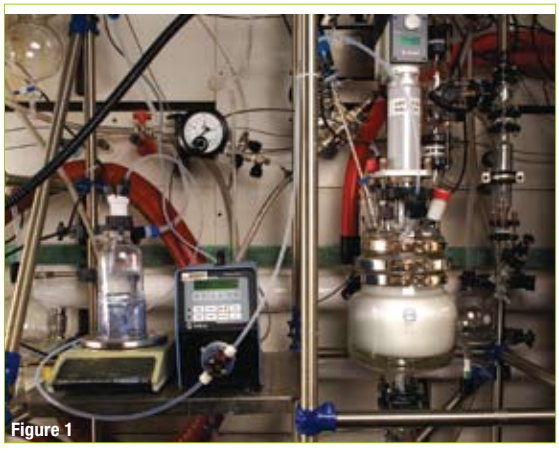
Figure 1


Figure 2

Figure 1: A 2-L jacketed lab reactor (JLR) with a dosing bottle on a scale at left.

Figure 2: A 2-L reactor with associated vapor trap (right) and distillate receiver (the glass ball). An insitu IR probe is inserted into the vessel on the left via a glass adapter (blue cap).

Another advantage of using a jacketed lab reactor is safety. Flanagan points out that product is removed from a lab reactor through a valve in the bottom of the vessel, whereas a flask is usually emptied by picking it up. "It can be dangerous to pick up a 22 L flask, and if you heat up a flask using a traditional mantle and the reaction starts to run out of control, there's no way to cool it." Although GSK has used jacketed lab reactors at some sites for several years, during 2005 and 2006, Flanagan led a multisite group to formalize the implementation of the technology in all of the company's five major research centres. GSK continues to improve the use of the technology through a laboratory reactor "site champions group" that has a representative from each of them. The Research Triangle Park (RTP) operation is one of two US headquarter sites for GSK, the other being in Philadelphia, where the company has one of its pilot plants. RTP has about 7000 employees, of whom some 3000 work in Research and Development. Chemical Development at RTP is a relatively small department, with about 150 employees, but it has developed processes for some high-profile drugs, such as AZT, Valtrex, Zyban and Avodart, for prostate treatment. At any one time, the department may be working on 15–20 projects.

Scaled-Down Pilot Plants

Chemical Development has 29 jacketed lab reactors, all supplied by De Dietrich Process Systems, Inc. (De Dietrich calls them Miniplant reactors). GSK also uses De Dietrich pilot-scale reactors in its pilot plant operations in Philadelphia. Using equipment from the same manufacturer at both the development and pilot stages makes for a smooth transition in the scale-up of a process, says Flanagan. "Our lab reactors are scaled-down versions of our pilot plant vessels," he says, "just as our pilot plants are scaled-down versions of production equipment." The 29 jacketed lab reactors at RTP consist of 13 1–6L, six paired 20 L kits and two paired 50 L kits. The smaller reactors are made of durable borosilicate glass and most are elliptical in shape, rather than round-bottomed, so their mixing characteristics are similar to those of a typical production-size reactor. A couple of conical-shaped vessels have also been installed for specialized studies. The 50 L kits are made of glass-lined steel and Hastelloy, identical to those found in pilot plants. The head of each lab reactor has a large central port for the agitator motor, which has either a single or double mechanical seal to ensure that the vessel contents are not compromised during operation. Other ports are available for purposes, including the addition of reactants and materials, a glass riser for distillation overhead, a thermowell for temperature measurements and other PAT functions.

In the glassware above the reactor is a manual valve that allows either reflux or removal of distillate. Each of the small reactors has a graduated receiver for distillate, but each pair of 20 L and 50 L vessels shares a single condenser and set of valves that allow distillate to flow from one vessel to the other. "This gives us the flexibility to reflux or distil from either vessel throughout the entire process," says Flanagan. "There is also a phase separator between them, so we can perform an azeotropic removal of water and direct either phase to either vessel." Product is removed through a valve at the bottom of the vessel — a manual valve on the smaller reactors and a pneumatically operated valve on the 20 and 50 L units. The design of the valve minimizes dead space and makes for a free flow of product through the valve, so that the product can be completely evacuated.

Work on new drugs starts in RTP's Drug Discovery Department, where potential drug candidates are made in quantities of up to a few grams in standard glassware. Those that show promise are moved on to Chemical Development, where processes to make active ingredients are scaled-up to produce quantities up to 100 grams in 1 or 2 L jacketed lab reactors. It is at this scale that most of the process development is done and basic problems are solved. "In these smaller reactors, we devote almost 100% of the work to process development and very little to


Figure 3


Figure 4

making material to support studies," Flanagan says. "When we scale up to the 6 L and 20 L reactors, we are probably down to 30% development, and when we get to the 50 L scale, 90% of the work is for the production of material for testing … and we are just tweaking the process." The use of jacketed lab reactors has also enabled GSK to develop GMP (Good Manufacturing Practice), clean-in-place and cleaning verification procedures as a process is scaled up. In addition, the company has performed equipment qualification exercises on all the lab reactors that are used for clinical material preparations.

Identifying Problems Early

Flanagan cites a number of examples when the jacketed lab reactors have revealed problems in the early stages of process development. "There have been cases where we have identified balling issues in our small reactors that we may not have seen in round-bottomed flasks." The

Figure 3: A scientist drains product from the manual bottom valve of a 2-L JLR.

Figure 4: A pair of 50-L, glass-lined steel JLR's with shared overhead glassware.


Figure 5

Figure 5: A pair of 20-L JLR's with shared overhead glassware.

Figure 6

Figure 6: Close-up of a 20-L JLR with a glass-lined, retreat-curve (similar to production vessels) and a pneumatically operated bottom valve.

reason, he says, is that mixing is done in a flask by a stir bar or paddle, whose mixing action is different from that of an agitator in a reactor. "The effect of agitation with a miniature agitator is similar to that of a full-scale plant agitator in terms of power per unit and shear effects," he says. "You can also model your process to use real heating and cooling times to get a more realistic demonstration of the process on a small scale."

Other cases have involved heterogenous reactions that use heavy, solid catalysts such as zinc-based or base metal catalysts that tend to settle to the bottom of the vessel. These processes "may work beautifully in a round-bottomed flask" because the stir bar or paddle is in contact with the bottom of the flask and grinds up the metal, says Flanagan. By contrast, the agitator in a reactor is not in contact with the bottom of the reactor, so the mixing is not as efficient. "Now, when we identify that kind of problem in a lab reactor, we work with our engineers to ensure that the appropriate geometry is selected for the scale-up of the agitator or of the reactor," he says.

Phase separations can also create problems when a process is stepped up from a flask to a pilot reactor. Flanagan notes that the way to check a phase separation in the laboratory is to dump the contents of a flask into a separatory funnel, shake the funnel and wait for the phases to separate. However, this procedure gives no indication of how long the separation may take in a reactor, or whether agitation may produce emulsions, which is important information necessary for scale-up. The best way to obtain this information, he says, is to do the phase separation in a lab reactor that mimics the pilot and production equipment. The use of jacketed lab reactors has also enabled GSK to save considerable time by cutting back on the use of reaction calorimetry to support intermediate (10–50 L) scale-up. In the past, when RTP worked with flasks, each process was tested in a reaction calorimeter prior to scale-up beyond the 6 L size, says Flanagan. "Today, 90% of the time we don't use reaction calorimetry for initial scale-up. Instead, we use data collected from jacketed lab reactors." GSK obtains heat output data by monitoring process temperatures in the lab reactors, each of which has been characterized to determine its heat-transfer coefficient. Gas-flow monitors are installed on all the smaller vessels to measure offgases. "With reaction calorimetry, it usually takes my group a couple of days to run the tests and evaluate the data," he says, "but with already available data from the lab reactors we can do an evaluation in a couple of hours. We probably do 100 risk assessments per year, so we save about 200 days a year by not doing reaction calorimetry at this point in the development cycle."

For the future, Flanagan feels the reactors will prove to be valuable in helping GSK meet the challenges of the US Food and Drug Administration's Quality by Design (QbD) initiative. One goal of the initiative is to reduce the regulatory burden on industry (and the FDA's workload) by streamlining the agency's approval of changes in the manufacturing process for drugs already in production. As in any other industry, pharmaceutical companies are periodically motivated to modify a process to make it more efficient. However, the time and effort required to support such changes, and to get FDA approval, makes it difficult to justify, says Flanagan. QbD would make it easier by allowing a drug company to show that its knowledge of a process is broad enough to permit modifications safely. Through the use of the lab reactors, combined with process analytical technology (PAT), GSK already collects a broad range of data on its processes, says Flanagan, and this will be useful for QbD. The data provide a good understanding of the "design space" for each process, such as temperature limitations and other parameters, he says, "so we would have plenty of information to support a process modification." Pharma

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