Microwave Synthesis Units Cater to Drug Chemists

Customer requirements for control and reproducibility drive evolution of microwave ovens from basic lab workhorses to finely-tuned instruments

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Microwave ovens aren't just for heating up leftovers and popping popcorn. The same speed that makes them so convenient in the kitchen makes them just as alluring to medicinal chemists looking to cook reactions faster. Amazingly, until a few years ago chemists had to trek to the local home electronics store to pick up their Samsung or Sharp oven just like everyone else. Reactions were liable to blow the door off the machine and be impossible to reproduce. But they continued publishing papers, and instrument vendors took note. As a result, the last few years have brought pharmaceutical chemists an increasing array of safe, consistent microwave instruments designed with their needs in mind. Competition has driven costs down, forced a rapid pace of innovation, and brought microwave instruments to the brink of widespread uptake.

Speed is the driving force. Optimizing reaction pathways and constructing chemical libraries takes time. Reactions that might have to run 12 to 14 hours in a conventional oil bath may finish in 5 minutes under microwave stimulation. (See sidebar on p. 50 for an explanation of the underlying physics.) "You're talking about setting up a reaction, going to get a cup of coffee, and coming back [to find] the reaction's pretty much done," says Anil Vasudevan, research investigator, medicinal chemistry enabling technologies at Abbott Laboratories Inc., Abbott Park, Ill. "It often takes longer to set up a reaction" than to run it, he says.

Until the 1990s, microwave instrument vendors were producing machines primarily to digest food or environmental samples by bombarding them with extreme levels of microwave radiation. They faced three primary obstacles in developing more precise machines geared toward industrial synthetic chemists: safety, control, and reproducibility. Digestion instruments operate essentially like home microwave ovens, which produce an uneven microwave field. The result is hot and cold spots where field intensity is high or low; that's why home ovens (and digestion instruments) usually come with rotating carousels. In fact, reactions run in home microwave ovens produced different yields depending on where the sample was placed, says James Empfield, associate director of lead optimization, central nervous system, and pain at AstraZeneca, Wilmington, Del. Users also had little control over the temperature or pressure of the reaction in a domestic microwave oven.

Home to the lab
Basic safety and control features became standard in the new wave of instruments. Infrared sensors monitor reaction vessel temperature, while pressure sensors of various kinds (pneumatic, piezoelectric) allow the machines to spot buildups. If the pressure climbs too high, vessels burp open and reseal or gases escape from ports in the cavity, while temperature falls to establish a safe pressure. Interlocks between the door and magnetron are designed to keep microwaves contained at all times. Software for programming reaction conditions allows chemists to repeat the same reaction with the same results. Users simply punch in the desired sequence of temperatures and the duration and maximum pressure for each step. The instrument adjusts the power coming out of the magnetron to maintain the proper temperature.

Milestone Inc., Monroe, Conn., stayed with the multimode design, but introduced an adapted version in 1997 with an eye toward laboratory use. Its current Microsynth Labstation, which costs $30,000 to $35,000, combines the microwave energies of two magnetrons in a premixing compartment to one side of the main reaction cavity. A metallic, propeller-like vane, called a "mode stirrer," churns the microwaves into a chaotic mishmash. The company also offers stir bars and other accessories made of a graphite-infused Teflon, which heats up in a microwave field and aids uniform heating. Milestone's device was the first commercial product that Boehringer Ingelheim Pharmaceuticals Inc. (BI), Ridgefield, Conn., purchased for laboratory use that was actually safe, says Christopher Sarko, senior principal research scientist at BI. "You could use it without having to worry about having the safety people up in arms," he says.

Multi-mode to single mode
Multimode cavities are primarily useful for larger samples, because smaller samples may feel the field only weakly, if at all. To satisfy chemists who wanted to work with one or a few milliliters of solvent, other vendors switched to a so-called single-mode...
### Heterocycles via enamino ketones

![Click to enlarge](image1)

**Improved scope of the Buchwald-Hartwig reaction**

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Though the extensive automation gave it a hefty $300,000 price tag, it also provided exactly what some chemists were looking for at the time. "When I got into microwaves, there were two very separate instrumentations: microwave heating and liquid handling," says Dean Wilson, medicinal chemistry group leader at Vertex Pharmaceuticals Inc., San Diego. "Personal Chemistry revolutionized [microwave chemistry] by linking it to robotics. That was something very fundamentally new and, in my opinion, very powerful."

The Smith had drawbacks, though. It attracted combinatorial chemists, but didn't meet their throughput needs, because it ran reactions sequentially. And for medicinal chemists, who wanted to synthesize novel compounds, the device was too complicated. Customers said it had to better match their existing infrastructure and workflow, said England.

### A modular approach

The Discover reaction vessel by CEM Corp., Matthews, N.C., followed hot on the Smith's heels. To maintain a well-tuned cavity in the presence of sealed reaction vessels, engineers designed a series of slots or windows around the reaction staging area, says Doug Ferguson, director of CEM's life sciences division. As microwaves emerge from the magnetron and circle the slotted wall, the sample pulls the field through specific slots, depending on its chemistry. CEM envisioned a modular platform from the beginning, building from the core Discover reactor, says Ferguson. Add-ons would address different market needs, keep costs down, and allow users to add functions indefinitely. At an average cost of $20,000. Discover suddenly made single-mode microwave instruments look affordable. "CEM entered the market with a simple instrument that lacked bells and whistles," says Wilson. "It was mechanically simple, the controls were simple, and the price was much lower. That had an important impact. It engendered a lot of competition." Its modular design gave chemists flexibility to pursue different approaches, he adds.

Personal Chemistry's engineers had returned to the drawing board, and in 2001 they introduced what would become the Emrys Creator. ("Smith" is impossible to trademark.) The footprint was reduced to fit fume hoods, and users now had to introduce samples by hand, but the price fell to $40,000, and currently stands at around $25,000.

Automation came next. Because reactions that finish every five minutes are tedious to switch out, Personal Chemistry reintroduced its transfer robotics in the Emrys Optimizer. The instrument contains its own reactor and includes robotics for automated sequential transfer of reaction vials in sequences of up to 60 vials, limited in speed by the heating and cooling time of a sample. The Liberator followed at the end of 2002 as a focused library synthesis platform to replace the Smith Synthesizer. A single user can control several Liberators from one server.

CEM's answer to automated reaction handling was the Explorer module, which includes a 24-sample deck, interchangeable racks and unlimited queuing of racks. Milestone's door and vessel technologies have made automation impractical so far, and customers have not demanded it, says Kenneth Borowski, technical manager for Milestone and physical-analytical chemist. Instead, the company focused on developing new reactor vessels for different applications.

### Meeting customer needs

The mechanical reliability of robotics and other design features was initially a problem, but has improved the past few years. Early on, says Sarko, "you could do three or four reactions..."
and the robot arm would die. Now you could do 100 with no problem.” In one machine, a needle that punctured the rubber septum on top of vials to measure their internal pressure would often become occluded and give bad readings after 10 or 15 reactions, says Vasudevan. Vendors addressed that problem, he says, and made cavities easier to clean after the occasional leak or broken vial. Some units at Abbott have run more than 4,000 reactions with only routine maintenance, and instruments have become better at handling higher power outputs, adds Daryl Sauer, senior group leader, high-throughput organic synthesis.

The choice of instrument depends on the application, says Sarko. Chemists at BI, like many users, customize their instruments. Sarko says he has seen different companies equip their instruments with IR spectrometers in flow cells to monitor reactions in real time, carousel robot feeders to load many hundreds of samples in sequence, and robots to analyze finished samples to determine if a reaction is done or not. Because sample preparation and work up are greater bottlenecks than reaction speed with microwave instruments, Sauer says that Abbott chemists have built additional robotics around their Personal Chemistry instruments to disperse liquids, cap vials, work up reactions and analyze products. “Everyone has a cute little invention,” says Sarko. “It depends on what you think is a need in your company.” Vendors rely on such customization to see what users want, he says. CEM, for example, introduced a modular Raman spectrometer for in situ reaction monitoring, called the Investigator, in response to customer requests for analytic instruments.

Two features that many chemists desire are parallelism and greater scale up. Parallel reactions cut time. A hundred reactions run sequentially in a microwave instrument might still take 24 hours. Running them all at the same time would take a few minutes. At first, Sarko says BI chemists used CEM’s Navigator module, designed for high-throughput synthesis, which can place finished reactions into 96-well plates. Hungry for more, they developed a sealed triple-96-well plate system, which allows reactions to attain high pressures and temperatures.

The difficulty in running 96 completely different reactions is that “each one wants its own intensity of field and has its own needs,” says Ferguson; highly absorbing reactions will steal energy from poorly absorbing ones, making field uniformity more difficult to achieve. He says parallel reaction control is an ongoing project at CEM. Personal Chemistry developed a proprietary technology for running microwave reactions in parallel, says England. He says engineers designed a machine that could independently control dozens of wells, but the company has not brought it to market.

**Addressing scale-up**

The latest microwave instruments can produce up to kilograms of compound, but scale up to hundreds of kilograms or tons is out of reach right now. "That's one of the holy grails," says Wilson. "One thing that really terrifies the average medicinal chemist is they adopt this new technology of microwaves and discover this amazing compound you just can't [scale up] conventionally."

BI chemists first tried optimizing reactions in a single-mode machine and scaling them up in a multimode, but the reactions didn't always work the same way in the larger machine. So, Sarko's group rigged up a flow cell for a single-mode instrument. CEM released the single-mode Voyager instrument at about the same time, in early 2003. Voyager can run in either continuous or stop flow formats. The stop flow format, which Ferguson says is more popular, can perform reactions in 100 mL of sample at a time. Milestone has released the MRS Batch Reactor, which takes a 380mL vessel, and the continuous flow, multimode Pilot-4000 Labstation, designed to pump 100 mL of sample each minute.

Personal Chemistry switched to a multimode design for scale up with the Emrys Advanced, which runs batch reactions in a 300 mL vessel. The field tuning mechanism and strong stirring help ensure uniform heating, says England. The company reports its chemists have successfully run a kilogram of product in a solid, crystalline precipitate, which would betray any uneven heat distribution. Several pharmaceutical companies have placed orders for the custom machine, says England, and serial production will depend on market response.

CEM engineers are working on scaling up beyond kilograms. The limited penetration of microwaves, about 2.5 cm, is one major engineering challenge. With microwave heating, "The chemistry is much more inhomogeneous than with traditional heating methods. A reaction might be hot on the outside but cold inside, and vice versa," explains England.

**Medicinal chemist at work.** (Source: Personal Chemistry)

with solid or viscous components, 80 mL at a time. Milestone has released the MRS Batch Reactor, which takes a 380mL vessel, and the continuous flow, multimode Pilot-4000 Labstation, designed to pump 100 mL of sample each minute.

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Microwaves heat samples in two ways. They are a type of electromagnetic field, so they're made of perpendicular electric and magnetic waves. An oscillating electric field will tend to tilt polar molecules such as water back and forth. If the frequency of the field is too high, the molecule won't have time to respond. If the frequency is too low, all the molecules will move precisely in time with the field and no heating will result. In the right range, however (around 2.45 GHz, the frequency set aside for microwave ovens and lab instruments) the molecules will lag behind the field. This lag causes them to dissipate microwave energy in the form of heat. The second mode of heating comes from ions jiggling back and forth in the electric field. That additional effect is why a glass of tap water heats up much faster than distilled water in a microwave. Some researchers have claimed to observe "non-thermal" microwave heating effects. Other chemists haven't been able to corroborate such reports, and in most cases can explain them by the usual mechanisms. Because microwave heating occurs directly in the sample and isn't conducted via the vessel wall, it is also highly uniform.
obstacle. A traditional continuous flow system pumps liquid through small-bore tubing, says Ferguson, but scaling up could involve much larger pipes running through multiple microwave cavities. Such an approach could allow sufficient resonance times, or exposure of sample to microwaves, and take care of moving solid reagents or products around. "The other philosophy is bigger static batches, which have safety problems," he says. Pressure mounts rapidly with increasing surface area, so safety would become increasingly difficult to maintain.

Difficulty in scaling up is a concern for any synthetic method and isn't necessarily a showstopper for microwaves, says Wilson, though "the risk of creating a process nightmare is still a barrier to adoption." Chemists at Abbott have yet to run into problems scaling up their microwave compounds, says Sauer. "I guarantee if we found a compound that could only be made by microwaves, our process people would become very involved very rapidly," he says.

The cost of single-mode microwave instruments has fallen substantially, but some chemists say the price (and footprint) could fall further. Personal Chemistry serially produces its instruments, but the company recently merged with Biotage AB, Uppsala, Sweden, which mass-produces flash chromatography instruments, to increase production at lower cost. CEM has projects to reduce cost and footprint in their next generation of instruments, says Ferguson, and offers the more spartan Discover Benchmate for $11,000 to $13,000.

Some chemists also see a need for better informatics tools to aid chemists in sharing results and conditions of reactions. Personal Chemistry offers software for storing and searching reaction conditions, converting search results into experiments, and capturing data after a reaction, but the programs are expensive, says Vasudevan. CEM and Synthematix Inc., Research Triangle Park, N.C., recently announced a collaboration to create a microwave reaction database and lab notebook, which may provide the solution if it is flexible and cost-effective, he says.

Ultimately, the number of chemists in the industry limits the market for microwave instruments, and thus the number of vendors. Nevertheless, microwave vendors remain highly competitive. "They talk to their customers," says Wilson. "They're working very hard to corner the market. The microwave instrument market was different in 2003 than it was in 2002, which was different than 2001." No doubt, it is changing as we speak.