

Microwave-enhanced Chemistry – Enabling Technology Revolutionising Organic Synthesis and Drug Discovery

a report by

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Background

Improving drug research and development (R&D) productivity is one of the greatest tasks facing the pharmaceutical industry. Many of the top pharmaceutical companies need to deliver innovative products in order to maintain top-line sales growth. In the next 10 years, the pharmaceutical industry will see many patents of drugs, currently generating a total of some US\$91 billion in sales, expire. In order to remain competitive, pharma companies need to pursue strategies that will offset the sales decline and see robust growth and shareholder value.

The top pharmaceutical companies are now looking for products that can generate at least US\$1.6 to US\$2 billion of new sales every single year.¹ That equates to up to four blockbusters – products with sales of between 500 million and one billion – a year. At the same time, the cost of developing a drug today is approximately US\$700 million, and the US Food and Drug Administration (FDA) estimates the average development time to still be approximately 10 to 15 years. Both cost and development time are unacceptably high for maintaining an industry growth rate of 10%.

The impact of genomics and proteomics is additionally creating an explosion in the number of drug targets. Today's drug therapies are based solely on approximately 500 biological targets while, in 10 years' time, the number of targets could well reach 10,000. In order to identify more potential drug candidates for all of these targets, pharmaceutical companies have made major investments in high-throughput technologies for genomic and proteomic research, combinatorial chemistry and biological screening. However, lead compound optimisation

and medicinal chemistry remain bottlenecks in the drug discovery process. Developing chemical compounds with the desired biological properties is time-consuming and expensive. Consequently, increasing interest is being directed towards technologies that allow more rapid synthesis and screening of chemical substances to identify compounds with functional qualities.

Microwave Synthesis

A new technique that is set to revolutionise synthesis has recently moved to the forefront of chemical research – microwave-assisted organic synthesis (MAOS).²⁻⁴ While fire is now rarely used in synthetic chemistry, it was not until Robert von Bunsen invented the burner that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the isomantle, oil bath or hot plate as a source of applying heat to a chemical reaction.

Microwave technology has been used in chemistry since the late 1970s, but it has only been implemented in organic synthesis since the mid-1980s. The slow uptake of the technology has been attributed to its initial lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating. However, since the late 1990s, the number of publications related to MAOS has increased dramatically to a point where it might be assumed that, in a few years, most chemists will probably use quick bursts of microwave energy to heat and drive chemical reactions.^{4,5}

As of 2003, many of the top pharmaceutical, agrochemical and biotechnology companies were already using MAOS as a forefront methodology for library

1. Nitin Naik, "Brave New Biotechnology World Revisited", Business Briefing: Future Drug Discovery 2002, London: World Markets Research Centre Ltd, October 2002, pp. 20–25.
2. D Adam, "Microwave Chemistry – Out of the Kitchen", *Nature*, 421 (2003), pp. 571–572.
3. For more information on microwave synthesis and equipment, see <http://www.maos.net>
4. P Lidström, J Tierney, B Wathey and J Westman, "Microwave Assisted Organic Synthesis – A Review", *Tetrahedron*, 57 (2001), pp. 9,225–9,283.
5. B Hayes, *Microwave Synthesis – Chemistry at the Speed of Light*, Matthews, North Carolina: CEM Publishing, 2002.

synthesis and lead optimisation, as they realise the ability of this enabling technology to speed chemical reactions. Not only are microwaves sometimes able to reduce chemical reaction times from hours to minutes, but they are also known to reduce side reactions, increase yields and improve reproducibility.

Theory and Equipment

Almost any type of organic reaction requiring heating or thermal conditions can be performed using microwave radiation. Microwave dielectric heating is dependent on the ability of a solvent or matrix to absorb microwave energy and convert it into heat.^{4,5} The matrix absorbs the radiation via two mechanisms: dipole polarisation and conduction.

When irradiated at microwave frequencies, the ions or dipole of the sample align in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have time to realign, or reorients too quickly with the applied field, no heating occurs. The allocated microwave frequency of 2.45GHz used in all commercial systems lies between these two extremes and gives the molecular dipole time to align in the field, but not to follow the alternating field precisely.

Microwave irradiation produces efficient internal heating (*in situ* heating), resulting in even heating throughout the sample, as compared with the wall heat transfer that occurs when an oil bath is applied as an energy source. Consequently, the tendency towards the initiation of boiling is reduced, and superheating above the boiling point of the solvent is possible even at atmospheric pressure. Superheating can be generated rapidly in closed microwave-transparent vessels to temperatures as high as 100°C above the normal boiling point of a particular solvent.

It is this combination of rapid microwave heating and sealed vessel technology that is responsible for most of the observed rate enhancements seen in MAOS, based on the well-known 'rule of thumb' that for every 10°C increase in temperature, the rate of the reaction is approximately doubled. It is possible, however, that macroscopic or microscopic hotspots resulting from the selective heating of specific reagents or catalysts can develop, leading to even faster conversions and the realisation of chemistries that cannot be conducted by conventional heating.

Evidently, more research is required to investigate the underlying principles of this heating method. Regardless of the exact origin of the observed rate enhancements, microwave synthesis is extremely efficient and applicable to a broad range of practical syntheses.

Although most of the early pioneering experiments in MAOS were carried out in domestic kitchen microwave ovens, the current trend clearly is to use dedicated instruments for chemical synthesis.²⁻⁴ Most of today's commercially available microwave reactors feature built-in magnetic stirrers, direct temperature control of the reaction mixture with the aid of fibre optic probes or infrared sensors and software that enables online temperature and pressure control by regulating the microwave output power. Since 2003, suppliers of microwave instrumentation for organic synthesis have also moved towards combinatorial/high-throughput platforms, addressing the needs of the drug discovery industry.³

Currently, two different philosophies with respect to microwave reactor design are emerging: multimode and monomode reactors.^{4,5} In the multimode instruments, the microwaves that enter the cavity are being reflected by the walls and the load over the typically large cavity. A mode stirrer ensures that the field distribution is as homogeneous as possible. In the much smaller monomode or single-mode cavities, only one mode is present and the electromagnetic irradiation is focused directly through an accurately designed wave guide onto the reaction vessel, mounted at a fixed distance from the radiation source.

For high-throughput applications, the key difference between the two types of reactor systems is that, whereas in multimode cavities several reaction vessels can be irradiated simultaneously in multi-vessel rotors (parallel synthesis), in monomode systems only one vessel can be irradiated at a time. In the latter case, high throughput can be achieved by integrated robotics that move individual reaction vessels in and out of the microwave cavity (automated sequential synthesis).

Productivity Increase – Time is Money

The bottleneck of parallel synthesis is typically connected with the optimisation of reaction conditions to afford the desired products in suitable yields and purities. Since many reaction sequences require a heating step for extended time periods, these optimisations are often difficult and time-consuming.

Microwave-assisted heating has been shown to be an invaluable optimisation method, since it reduces reaction times dramatically, typically from days or

hours to minutes or seconds.⁶ Many reaction parameters can be evaluated in a few days to optimise the desired chemistry. Compound libraries can then be synthesised rapidly using the new technology, either in a parallel or sequential mode.

Several large pharmaceutical companies have reported dramatic productivity increases in switching from conventional synthesis to MAOS.^{7–12} Although the initial investment costs are considerable, the dramatically increased efficiency of the microwave approach allows a return of investment in a short timespan. This has prompted several pharmaceutical companies to install multiple microwave reactors in their R&D laboratories, in some cases even eliminating oil baths and heating mantles from their laboratories.

The success stories of MAOS in the drug discovery process are manifold and have been documented in several articles involving both target and lead discovery, lead optimisation and drug development.^{6–12} With the most recent advances in reactor technologies, such as continuous-flow microwave systems, even process chemists are now taking MAOS seriously. Chemistry applications have ranged from conventional solution phase synthesis to protocols involving polymer-supported reagents or scavengers, in addition to solid or fluorous phase techniques.^{6–12} Most recently, microwaves have also been used to speed up biochemical processes such as polymerase chain reaction or enzyme-mediated protein mapping. The full scope and potential of this technology may not yet have been realised.

Obstacles to Acceptance of the Technology

Given the advantages of microwave synthesis, it might be surprising that not everybody is using it. One of the possible reasons for this could be mental inertia, as the use of this new technology requires a change in the chemist's mindset, abandoning the traditionally favoured tools of the trade such as heating mantles, oil baths or hot plates for something different.

Another factor that is certainly holding the field back is prices. The least expensive of the new generation of microwave reactors currently sells for about US\$20,000, which is beyond the buying power of many laboratories. More elaborate systems geared towards the drug discovery industry that have integrated automation and liquid handling capabilities, database and electronic laboratory functionalities or an added scale-up option involving continuous flow cells are considerably more expensive. Despite this fact, it is clear that microwave synthesis is an enabling technology that is here to stay. In five to 10 years, there will probably be a microwave reactor in every academic and industrial laboratory. They will truly become the Bunsen burners of the 21st century. To quote the French novelist and poet Victor Hugo:

“There is one thing stronger than all the armies in the world, and that is an idea whose time has come.”

The time for microwave synthesis certainly has arrived. ■

6. M Larhed and A Hallberg, “Microwave-assisted High Speed Chemistry: A New Technique in Drug Discovery”, *Drug Discovery Today*, 6 (2001), pp. 406–416.
7. D Bradley, “They Nuke the Thing for Synthesis. In *Combinatorial Chemistry, the New Wave is Micro*”, *Modern Drug Discovery*, 4 (2001), pp. 32–34 and 36.
8. G Roth and C Sarko, “Microwave Energy Speeds Organic Synthesis”, *Drug Discovery and Development*, September 2001, pp. 57–58.
9. B Wathey, J Tierney, P Lidström and J Westman, “The Impact of Microwave-assisted Organic Chemistry on Drug Discovery”, *Drug Discovery Today*, 7 (2002), pp. 373–380.
10. C O Kappe, “High-speed Combinatorial Synthesis Utilizing Microwave Irradiation”, *Current Opinion in Chemical Biology*, 6 (2002), pp. 314–320.
11. G Dutton, “Employing Microwaves to Accelerate Synthesis”, *Genetic Engineering News*, 22 (2002), pp. 12, 15 and 17.
12. K J Watkins, “Up Close & Personal – Chemistry, That Is. Sweden’s Personal Chemistry Uses Automated Microwave Systems to Speed Drug Development”, *Chemical and Engineering News*, 80 (2002) 6, pp. 17–18.