# Microwave-assisted synthesis in the pharmaceutical industry

## *a current perspective and future prospects*

In the past five years there has been a dramatic upsurge in the use of microwave heating within the pharmaceutical industry to facilitate the chemical synthesis of new chemical entities. The increased uptake of this technology has been catalysed in part by the observation that reaction rates for the best cases could be accelerated 1,000-fold. New technology, in the form of commercially available single-mode microwave systems as well as recent advances in multi-mode commercial laboratory unit technology, has fuelled the introduction of this technique into pharmaceutical R&D synthesis chemistry laboratories. This paper will provide an overview of the currently available options for conducting microwave-assisted synthesis in pharmaceutical R&D from discovery through development. Future prospects for this nascent technology will be explored; especially with respect to the outlook of this technique as it moves from the bench-top to scale up.

**By Dr Richard Wagner**

Over the past five years there has been a dramatic uptake in the use of microwaves as an energy source to promote synthetic transformations. The production of dedicated instrumentation by the major vendors has propelled what was 20 years ago an intriguing concept into a day-to-day tool for synthesis chemists. Microwave-assisted organic synthesis (MAOS) is clearly a method by which the laboratory chemist can achieve goals in a fraction of the time as compared to traditional conductive heating methods. Reactions times in the best cases have been reduced from hours or days to minutes. This technology has been described as both enabling and disruptive. With the extraordinary progress made recently in this field it is fair to ask: what does all this mean and of what importance is this scientific and technological advancement with respect to addressing the pharmaceutical industry's chief concerns?

Of paramount importance to the pharmaceutical industry is the identification of methods by which increased efficiency can be achieved in the

drug discovery and development process[1]. The putative benefit of enhanced efficiency includes a reduction in product development lifecycle with a concomitant increase in the number of new pharmaceuticals introduced to the marketplace. From the standpoint of synthesis chemistry, the use of microwaves as an energy source to heat reaction solutions has been shown to provide the following advantages:

- Broad applicability – few limitations as to types of synthesis chemistry.
- Increased reaction rates – 1,000-fold in best cases.
- Used to accelerate chemistries in both solution and solid-phase reactions.
- Improved product yields.
- Moderately scalable (sub-milligram to multigram quantities).
- Can be conducted in either open or closed vessels.
- Access to synthetic transformations not achievable via conductive heating.
- Broad dynamic temperature range (-45°C to 300°C).
- Green chemistry – reactions in supercritical water or solvent-less reactions.
- Can be used to accelerate the synthesis of peptides.
- Controlled method of heating.
- Rapid reaction optimisation.

One might conclude that reduced reaction times and many of the other advantages offered by microwaves as an energy source confer increased productivity and ultimately enhanced efficiency. If this is truly the case then one may ask if the pharmaceutical industry synthesis chemist's first port of call is the microwave instrument for use as a source of energy in which to promote synthetic transformations.

The breadth and depth of applications for MAOS can be found in one of the numerous reviews and books on this topic[2-9]. The field has been driven by not only the curiosity of the chemists looking to expand the boundaries of this technique but also by the instrumentation companies that develop the kit for conducting MAOS (**Table 1**). At present there is a strong collaborative partnership between academic and industrial researchers and the instrumentation developers. This collegial atmosphere and the marketplace have resulted in the introduction of novel instrumentation and instrumentation refinement every year since 2001. The breadth of microwaves as an energy source for pharmaceutical industry applications is captured in **Figure 1**. MAOS has entailed much of the effort to date; however the term 'microwave-assisted life sciences' is applicable as microwaves as an energy source is starting to affect the research areas of proteomics and pharmacokinetics.

**Table 1:** Microwave instrumentation providers for MAOS

| |
|---|
| Anton Paar |
| Biotage |
| CEM |
| Milestone |

## Microwave heating vs conductive heating

Traditional or conductive heating relies on a thermal energy source directly applied to the reaction vessel. Conductive heating is inefficient and slow but is broadly applicable and conceptually straightforward. Basically, conductive heating gets the chemist where they want to go. However, the inefficiencies of ramping-up to temperature, lack of fine control over the bulk reaction temperature and the time needed for the cooling of the bulk reaction all impart disadvantages. The key caveat is that conductive heating of solutions has been the primary means of heating solutions during traditional synthesis chemists' training.

Conversely, microwave heating can be affected remotely, is rapid and for most is not conceptually straightforward. Reaction solutions are heated via the direct coupling of microwave energy with either the solvent or molecular entities in solution followed by rapid loss of the energy in the form of heat. The microwave energy is much less than the typical bond-dissociation energies of typical organic moieties. Because microwaves travel at the speed of light they can be turned off instantaneously upon reaching the temperature set point of the reaction solution. To heat efficiently the microwave energy must couple effectively with the reaction solvent of choice. Not all solvents absorb microwave energy equally well. In general solvents are categorised as high, medium or low absorbers and this in part characterises their ability to warm solutions via the absorption of microwave energy. The differential microwave energy absorptive rates for different solvents should not be viewed as a deterrent, as this technique allows for rapid reaction scoping and alternative reaction conditions can be rapidly identified.

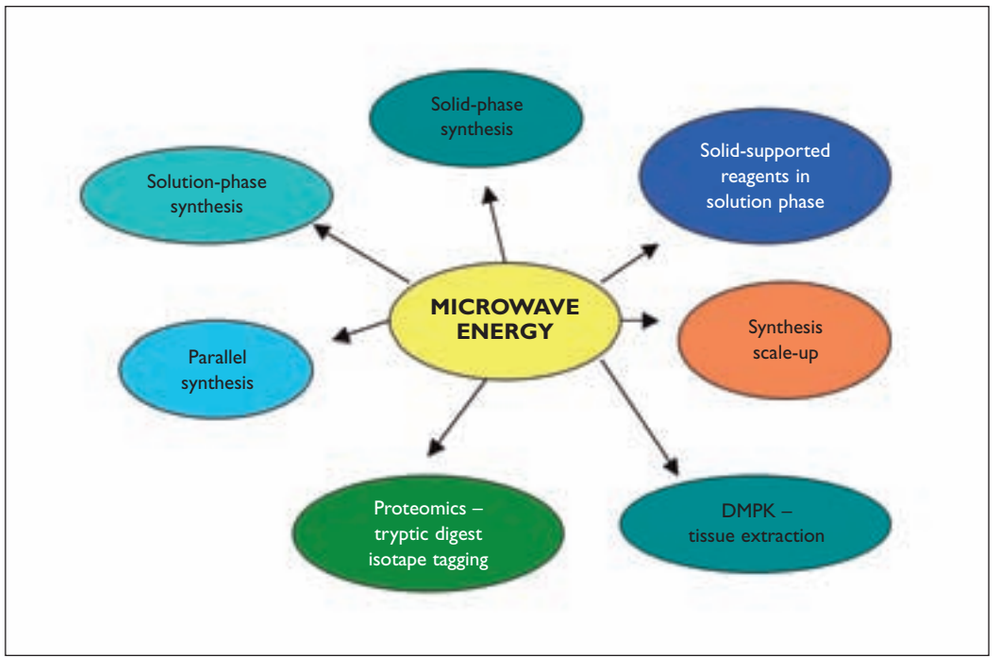


**Figure 1**
The breadth of applicability of microwave energy is highlighted

## Reaction optimisation

Reactions promoted via microwave energy are ideally suited for reaction scoping and rapid reaction optimisation. The reaction times in general are in the order of minutes. This timescale enables a facile and rapid scoping of reaction conditions in terms of the reaction parameters of time, temperature, reagents and solvents. Recent examples include the rapid optimisation of a diverse purine library in which the optimum conditions were rapidly identified and found to be in the order of minutes as compared to the traditional 12-24h timeframe[10]. The rapid nature of the technique also lends itself to the use of statistically designed experiments. An optimisation of the synthesis 1,2,4-oxadiazoles used statistical design to reveal the optimum reaction time to be 10min with a 2-10min limit set for the experimental design[11]. These examples of rapid optimisation reveal the power of microwaves as an energy source in scoping reactions and more importantly this can be used to rapidly identify routes to novel chemical entities. The incorporation of analytical tools as part of the microwave instrumentation in which real time data can be acquired will further aid in reaction optimisation.

## Microwave instrumentation dynamic range

The term 'microwave' is inextricably linked in our modern society to the rapid heating or warming of foodstuffs. What is intriguing from a synthesis chemistry standpoint is the dynamic range of temperatures afforded by today's dedicated laboratory microwave instrumentation (**Figure 2**). To date most of the effort has focused on elevated temperature transformations or reactions requiring heating. Synthetic transformations heretofore unachievable through conductive heating have recently been realised using microwaves as the energy source. Low temperature reactions via microwave energy have only recently been introduced with the key point being that gentler reaction conditions are now a consideration[12]. Gentler reaction conditions are especially important with respect to biochemical applications in which the preparation of peptides[13-14], peptoids and oligosacharides[15] are of interest.

Heating water in a closed vessel well above its boiling point produces supercritical water (**Figure 2**). This form of water is less polar and thus more effective at dissolving organic substrates. In addition, the increased use of water in industrial settings is a popular notion in terms of 'green chemistry', as water is environmentally more benign than traditional organic solvents, cheaper and when used in this context provides for facile separation of the solvent and organic reactants and products[15].

## Microwave instrumentation

The advent of microwave-assisted organic chemistry occurred 20 years ago[17-18]. The possibility of

enhanced reaction rates via microwave heating was intriguing but the routine adoption of this technique was stymied by the available kit for conducting routine synthetic transformations. Domestic microwave ovens were used for much of the initial work, however they were not built for organic chemistry, as they lacked pressure and temperature control, a mechanism by which to stir or agitate solutions and the multi-mode microwave cavity within a domestic unit creates 'hot and cold spots'. These features, especially for small-scale syntheses, resulted in synthesis conditions that were difficult to reproduce and in addition safety concerns were of paramount concern as volatile organic solvents were routinely excluded for fear of fire or explosion. These limitations severely inhibited the exploitation of the microwaves as a heating source until dedicated instrumentation was introduced.

The advent in 2001 of 'single-mode' microwave instruments dedicated to small scale (0.2mL to 5mL) synthetic chemistry rekindled the pharmaceutical industry's interest in MAOS. These dedicated instruments contained many of the features required for controlled and reproducible MAOS, which included: a homogeneous microwave field, magnetic stirring, pressure sensors for closed vessel reactions to avoid excessive pressure build-up and temperature sensors to control the rate and power of microwave irradiation which in turn provided for temperature control.

Multi-mode instruments were the original kit used to conduct MAOS. Dedicated laboratory multi-mode instruments with the appropriate safety features that incorporate feedback mechanisms for pressure and temperature are well suited for MAOS, especially for larger reaction volumes and parallel synthesis.

## Pharmaceutical industry applications

### Medicinal chemistry

The 'single-mode' instrumentation was initially introduced with medicinal chemists in mind. The ability to conduct small scale (0.2mL-5mL) reactions was viewed as ideal for lead optimisation. Rapid reaction scoping of a broader reaction space is accessible via microwave heating as compared to traditional methods and this was thought to be ideally suited for the identification of new chemical entities. The uptake of this technique initially was greater in the discovery or parallel synthesis groups. These groups tend to be more instrumentation and automation intensive than traditional medicinal chemistry laboratories. The juxtaposition of these groups within buildings has aided in the sharing of microwave instrumentation and in part has hastened the uptake of this technique.

### High-throughput chemistry and parallel synthesis

The mid-1980s witnessed the introduction of the field of combinatorial chemistry. The routine use of the mix and split methodology to produce pools of compounds has been largely abandoned by the pharmaceutical industry in favour of the synthesis of single pure compounds for high-throughput screening[19]. High-throughput synthesis methods exploit much of the automation, parallel sample handling techniques and high-throughput purification techniques developed during the vigorous investigation of combinatorial methodologies. These methods are an ideal complement to the implementation of MAOS high-throughput chemistry and MAOS parallel synthesis.

High-throughput chemistry or serial reaction processing can be conducted with pick and place automation in conjunction with a microwave energy source. Most of the 'single-mode' instrumentation

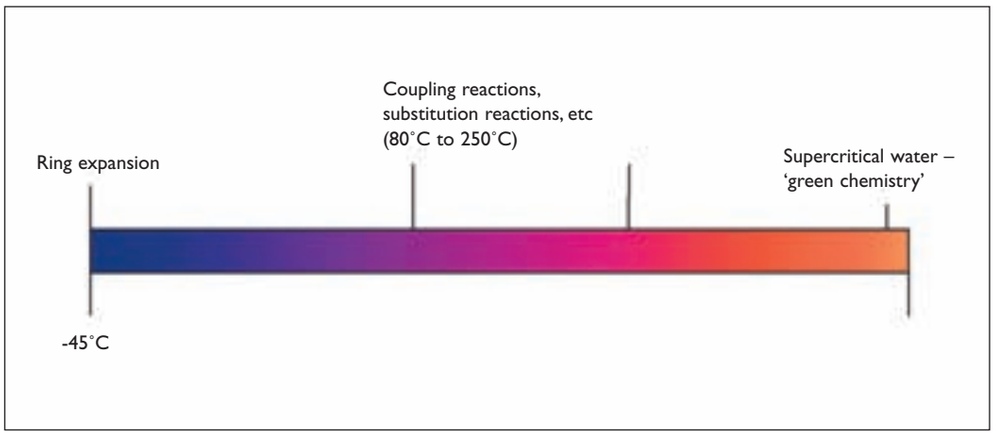


**Figure 2**
The available microwave instrumentation dynamic range is shown with general example shown to highlight the applications in a give temperature range. The chart is not intended to be linear but purely illustrative of the breadth of opportunity afforded by microwaves as an energy source

provides these features. This technique is often used in parallel synthesis laboratories or medicinal chemistry laboratories in which microwave instrumentation is shared.

Parallel synthesis can be performed in microtitre plates or systems in which multiple sealed-tube reactions can be placed on rotors (racks). Traditionally these parallel approaches have been carried-out in multi-mode systems. The breadth of chemistries ranges from heterocylces[2-9] to peptides[13-14].

**Process development**

MAOS in the context of process development has witnessed an increased focus over the past two years. The two approaches receiving the most attention are stop flow or batch processing and continuous flow. In batch processing the reagents are pumped into the microwave reactor, the reaction is run as per the predetermined parameters and following the conclusion of the reaction the reaction mixture is pumped out of the reaction vessel and into a collection container. To achieve multi-gram or kilogram quantities, this process must be repeated the requisite number of times to realise the desired amount of material[20].

Continuous flow systems are those in which the reaction mixture is continuously pumped through the microwave cavity. The maximum production of the desired product is dependent in part on achieving the optimum residence time within the microwave cavity. This approach has met with varying degrees of success, as the continuous-flow microwave instrumentation has difficulty handling heterogeneous reaction mixtures and viscous liquids[16,21-22]. To date there are no ideal solutions for MAOS process chemistry applications but it is early in the development cycle and continued focus on this area will most likely reveal practical solutions.

## Biosciences

The instrumentation developed for MAOS has more recently found application in what has been traditionally termed the biosciences. These areas include peptide synthesis proteomics and DMPK. Recent publications in the field of proteomics have shown the instrumentation used for MAOS can also be used to accelerate tryptic digests with the total time reduced from hours to minutes with a concomitant improvement in coverage. High-throughput proteomic applications may require the development of plate-based instrumentation to facilitate the work flow.

## Safety

Safety is of paramount concern not only with any chemical-based activity but especially where the irradiation of samples with electromagnetic radiation is concerned. The whole notion of reaction acceleration and rapid heating implies that additional safety issues must be addressed. In addition much of the chemistry is conducted within sealed vessels. The industry suppliers have addressed these issues through development of explosion proof reactors, shutdown mechanism for situations in which overheating or over-pressurisation occurs and venting mechanisms for closed vessel reactions.

## Future prospects

The advantages of microwaves as a source of energy for heating synthesis reactions have been clearly demonstrated. What is less clear, as with most new techniques or technologies, is what is the rate of uptake of this approach and what factors are affecting the implementation rate.

The use of microwave instrumentation to heat reactions is a paradigm shift for nearly all trained synthesis chemists. Until recently most academic laboratories did not practise this technique. Therefore the use of microwaves as an energy source requires a mind-set change or behavioural change in the way in which synthesis chemistry is practised. In addition there is a learning curve associated with using microwave instrumentation. Initial use requires familiarity with not only the instrument operation but also the translation of traditional reaction conditions to microwave conditions. With the rapidly expanding number of published examples and the readily available tips and tools that accompany commercial instrumentation the leap from traditional conditions to microwave heating is far less daunting than when the field began.

The current percentage of reactions being performed with microwaves as the energy source has not been quantified at the present time. Opinions differ but it is reasonable to estimate the rate of use

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in the pharmaceutical industry as between 10-25%. Clearly the usage of microwave energy to promote a diverse array of chemistry is on the increase. As with most instrumentation or automation in an industrial setting, the question remains: is it being used to the maximum extent possible?

The pharmaceutical industry is clearly under pressure to increase R&D productivity. MAOS is appealing in this regard, as it can increase the rate with which new chemical entities (NCE) can be synthesised. However the synthesis of NCEs is only one part of the overall process by which new pharmaceuticals are developed. An increasing rate of MAOS adoption must also be done concurrently with an overall process assessment. Increased synthesis throughput must be complemented with an increased throughput in the purification, isolation and characterisation processes.

The development of reliable MAOS tools for process development and potentially manufacturing are in the exploratory stages and may be needed as the field moves forward. The putative development lifecycle of new medicines is currently 12-15 years. The field of MAOS has genuinely taken off in the past five years. It may too early to ascertain if there are any compounds poised to enter clinical development for which microwave heating is the only process by which they may be synthesised. A microwave-only process for a potential blockbuster medicine may help spur investment in process MAOS capabilities. Microwave-assisted organic synthesis is no longer a curiosity but an enabling technology whose full potential has not yet been realised. DDW

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