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ULTRASOUND-MICROWAVE COUPLING:
AN EFFICIENT TOOL FOR CHEMICAL-PROCESS INTENSIFICATION

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Abstract. The intensification of chemical processes, which means improving their efficiency and cutting down energy consumption, requires more automation and non-conventional energy sources, as well as new, efficient and scalable protocols to be implemented in continuous-flow reactors. We showed that the specific advantages of microwaves and power ultrasound may become additive when they are used in combination, resulting in the optimization of both heat and mass transfer. We developed several reactors for combined irradiation, whether simultaneous or sequential, experimenting with new materials that are compatible with both techniques. We present here a series of applications to show that flow chemistry using hybrid reactors combining microwave and power-ultrasound units can really achieve process intensification as required by modern synthetic and environmental chemistry.

Key-words. Microwaves, power ultrasound, flow chemistry, intensification, green process.

The design and development of procedures for manufacturing fine chemicals or pharmaceuticals must conform to strict criteria concerning not only efficiency and selectivity, but also time frame, safety, costs and environmental impact. Similar criteria also apply to the treatment of polluted waters and sludges; in this regard the efficiency of time-consuming procedures should be strongly enhanced, as is done in advanced oxidation processes (AOPs). In these contexts the specific advantages of power ultrasound (US)[1] and microwaves (MW)[2], i.e. their ability to enhance reaction rates, yields and specificity, may become synergistic when they are used in combination. In the last decade much effort was devoted in our laboratory to designing and developing innovative US[3] and US/MW reactors[4].

INTRODUCTION

The application of power US to chemical processes[5] is one of several intensification methods that have been much developed over the past two decades. The driving forces for this trend are manifold, though, as emphasized above, an important factor is surely the increasing demand for an environmentally safer technology that minimizes the production of waste. Energy input by ultrasound does promote cleaner reactions by improving product selectivities and yields, as well as product recovery and purity through, for instance sono-crystallization[6] and US-assisted extraction processes[7]. Mechanical and chemical effects of US are caused by cavitation bubbles being generated at nucleation sites (sites containing some gaseous impurity) during the rarefaction phase of sound waves. Low-frequency US (usually in the range of 18-100 kHz) induces more violent cavitation, resulting in higher localized temperatures and pressures at cavitation sites. It has been estimated that these hot spots have temperatures of about 5000 K with cooling rates above 1×10^{10} K s^{-1}, and pressures of the order of 100 MPa[8]. The cavitational collapse can be considered as a quasi-adiabatic process. The kinetic energy released under these extreme conditions drives reactions to completion, also causing, along with shock waves at the bubble-liquid interface, the homolytic cleavage of molecules trapped inside the bubble. Although at higher frequencies (e.g. 300-1000 kHz) cavitation is less violent (hence higher intensities will be required to achieve effects comparable to those obtained at lower frequencies), the production of free radicals is greater, as more cavitational events occur, hence an increased chance for radical species to be produced. Probably, one of the most telling examples of true sonochemistry was the report by Ando and coworkers of a sonochemical switching in the reaction of benzyl bromide, potassium cyanide and alumina. This system, when stirred mechanically in

toluene at 50ºC, gave rise to a mixture of *o*- and *p*-benzyltoluene in 75% yield. In contrast, when irradiated with US (45 kHz) at the same temperature it afforded benzyl cyanide in 71% yield[9]. The reaction switch from a Friedel-Crafts to a nucleophilic substitution course was attributed to the acceleration by US of a specific poisoning by potassium cyanide of the catalytically active sites of alumina[10]. We also observed sonochemical switching in the selective C-monoalkylation of 4-hydroxycoumarin with allyl and benzyl halides in water[11] and the bromination of alkylarenes with NBS in water where US strongly favours ring substitution[12].

The dramatic accelerations of many chemical processes by MW are chiefly attributed to a more uniform heating compared to conventional procedures that generate large temperature gradients. Whereas cavitation is a complex phenomenon that involves fluid dynamics, MW effects are rooted in the well-known dielectric heating. Although one may suppose that the latter are better understood, thus explaining the explosive development of their applications in the last two decades, the reasons why MW are capable of enhancing chemical reactions is still not fully understood. It is generally accepted that in most cases, if not all, the observed effects are purely thermal, i.e. they result from the high reaction temperatures attained when polar materials absorb MW[13]. Specific thermal MW effects, which cannot be reproduced by conventional heating, are also invoked. These include: superheating of solvents above their boiling points at atmospheric pressure; selective heating of MW-absorbing reagents and catalysts, especially noticeable in less polar or apolar reaction media; and the absence of wall effects because of inverted temperature gradients[14]. In a very recent study, Kappe and his associates found no evidence for non-thermal MW effects in a re-investigation of four model reactions, in which they employed a multiple fiber-optic probe system for accurate temperature measurements in both MW- and conventionally-heated reactors. They also showed that an efficient agitation of MW-heated reactions is essential[15]. The large majority of MW-assisted reactions published till date have been performed on a less than 1 g scale, though for a fully acceptance of this technology there is a need to develop larger scale reactors that can ultimately routinely provide products on a multi-kilogram scale[16]. The penetration depth of MW at the typical operating frequency (2.45 GHz), is generally of a few centimetres, depending on the dielectric properties of the medium (in water, 1.4 cm at 25°C and 5.7 cm at 95°C), for this reason the reactor dimensions are limited[17]. This physical limitation is one of the main reasons for the development of MW continuous- or stop-flow reactors, where the reaction mixture is passed through a relatively small MW heated flow cell, which avoids penetration depth problems. Although the first prototype of MW flow reactor was already patented at the beginning of the '90s[18] only more than ten years later was the first equipment commercially available[19].

At first glance, the idea of combining microwave and ultrasonic irradiations looks odd, as they have a distinctive physical nature, quantum and non-quantum, respectively. While for an electromagnetic radiation (microwaves) energy and frequency stand in a direct relationship, the cavitational energy is not directly proportional to frequency. In fact, the relationship is rather complex due to nonlinear effects of cavitational collapse. Despite these considerations, if we ignore non-thermal microwave effects, purely thermal effects resulting from dielectric heating plus pyrolytic mechanisms and efficient stirring arising from cavitation can account for the observed enhancements. The effectiveness of combined irradiation is brought out by the synthetic examples offered below.

Another, practical aspect to be considered is the fact that simultaneous irradiation with MW and US involves technical difficulties and safety considerations. The ultrasonic energy generated by a transducer is usually delivered to the reaction vessel via a horn made of titanium alloy. A piece of metal placed inside a MW chamber would cause arcing and possibly result in vessel rupture or perhaps an explosion when flammable compounds are present. Electric arcs can also be formed in the cavity by an excessive input of microwave energy (the efficiency of MW absorption decreasing as temperature rises); therefore temperature, pressure, stirring rate and power input should all be monitored and controlled for safe operation. US can be conveyed inside a modified MW oven by inserting through its wall and down into the reaction vessel a horn made of quartz, even though this is far from the ideal material because of its fragility. Pyrex® also shares the same drawback, while ceramic horns may be more expensive.

Flow-chemistry is the last evolutionary step in synthetic chemistry[20]. In recent years, chemistry in flowing systems has become more prominent as a method of carrying out chemical transformations, ranging in scale from analytical-scale (microchemistry) up to kilogram-scale synthesis[21]. Its advantages are readily increased control of conditions often leading to greater reproducibility and scalability, increased safety and lower investment, although its acceptance as a viable synthesis technique has been limited by its drawbacks, such as liquid handling, and diffusion of the reaction within the reactor[22]. The use of solid-supported reagents and catalysts is advantageous as reaction products will alone remain in solution, thus enabling the reaction to be continually monitored, and easily optimized.

The aim of our work was to set up new flow reactors that could exploit the synergic effects of combined US/MW irradiation as a new, efficient tool for chemical-process intensification.

RESULTS AND DISCUSSION

In the design of new, more versatile sonotrodes to be used in combination with MW we experimented with several non-metallic horns/cup-horns and found that certain types of PEEK® had excellent acoustic properties. Figure 1 shows a prototype of "cavitating tube"[23] working at 22.5 kHz and made of PEEK® (containing a small amount of carbon fibers). This small device (holding up to 90 ml) is well suited for reactions under modified atmosphere, is very light, and does not need an insulation cage, because it is made of a polymeric material that minimizes the emission of audible, troublesome harmonics.

Using PEEK® containing a small amount of glass fibers we fashioned horns (Figure 2) to be inserted in the cavity of a MW oven, an excellent solution that overcomes the above-mentioned drawbacks of Pyrex® and quartz.
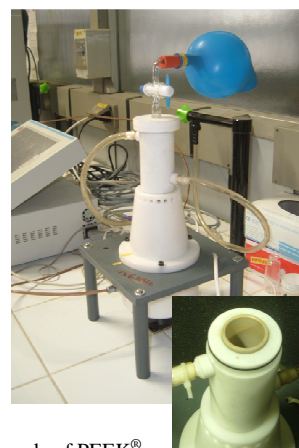

Figure 1. US reactor made of PEEK®

Although the intimate mechanisms of cavitation and MW effects are incompletely understood, as a rule processes requiring enhanced heat- and mass transfer will greatly benefit from these green techniques. However, when US and MW irradiation are combined (whether simultaneously or sequentially), operating conditions have to be tailored to each specific application for optimal results to be reaped. We recently reviewed applications of US/MW for process intensification[24] as well as the interesting synergies arising from the use of ionic liquids in this context[25]. Maeda and Amemiya can be considered as the originators of the technique[26], as they first described the synergic effect of simultaneous US/MW irradiation. Chemat et al. avoided subjecting the horn to the electromagnetic field by using decaline (a low-viscosity apolar liquid) to convey US waves inside the oven and to the reaction mixture that was placed in a double-jacketed pyrex vessel[27]. Peng and Song employed a modified domestic MW oven and inserted in it a probe fitted with a detachable horn (whose material, obviously not a conductor, was however unspecified by the authors)[28]. They used this set-up for a solventless hydrazinolysis of esters, to synthesize ethers (Williamson)[29], for Knoevenagel-like reactions[30] as well as Mannich reactions[31].

Our apparatus for simultaneous US/MW irradiation was employed for the one-pot synthesis of second-generation ionic liquids[32], particularly from poorly reactive alkyl chlorides[33]; for the selective reduction of nitroarenes[34] and oxidation of anilines[35], the regioselective opening of epoxides by nucleophiles in water[36], Heck reactions carried out with very low catalyst concentrations[37], and the US/MW-assisted extraction of natural matrices[23].

Figure 2. Simultaneous US/MW irradiation (horn made of PEEK®).

Figure 3. Loop reactor for sequential US/MW irradiation.

Our first US/MW flow reactor (Figure 3)[38] consisted of: 1) A probe equipped with a titanium horn (20.5 kHz) inserted in a thermostatted reaction vessel (also made of titanium); 2) A MW oven containing a loop of Teflon® tubing; 3) Two lengths of coaxial tubing and a peristaltic pump by which the reacting mixture is circulated between the US and MW units. 4) Another pump by which a cooling fluid

(Galden®), refrigerated by a chiller, is circulated in countercurrent through the outer compartment of the coaxial tubing. 5) Two thermocouples (inserted at the inlet and outlet of the MW oven).

In this flow reactor we successfully performed several kinds of reactions, in particular Pd-catalyzed C-C couplings including Suzuki homo- and cross-couplings, Sonogashira and Heck reactions[39], besides Ullmann, Barbier and Reformatzky reactions. The sonochemical activation of the metallic catalysts and the accelerating effect of MW heating, led in all cases to excellent results in terms of yield and reaction time.

Owing to the low penetration depth of US and MW (a few centimetres in both cases) and the high energy consumption, continuous stirred tank reactors (cascade system) are not suitable for combined US/MW irradiation.

Figure 4 shows a typical loop-reactor set-up working in our laboratory that allows either simultaneous or sequential US/MW irradiation by an easy shift of the horn (US probe). Two different US and MW units may clearly work at different temperatures. This stop-flow reactor can also be use as a semi-continuous reactor.
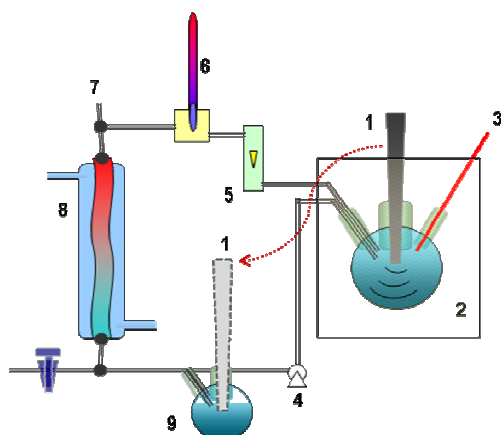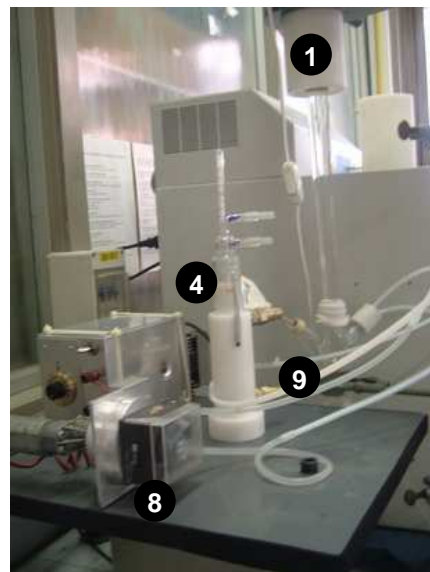

Figure 4. Stop-flow reactor for simultaneous (or sequential) US/MW irradiation (1. US non-metallic horn; 2. MW oven; 3. Optical fibre thermometer; 4. Pump; 5. Flow-meter; 6. Thermometer; 7. Inlet and sampler; 8. Heat exchanger; 9. External flask)

Figure 5. Stop-flow reactor in the sequential irradiation setup: the Pyrex® horn is inserted in the external flask (numbers refer to figure 4).

Successively we developed a larger semi-continuous US/MW flow-reactor[40] (Figure 6), a 5-liter prototype that included two sonotrodes working at different frequencies (20 and 300 kHz) and a MW oven. A centrifugal pump circulates the reacting mixture through the reaction compartments, the flow to the US and MW units are regulated by a valve before it is returned to the tank (loop system). Three thermocouples monitor temperatures at the outlet from the MW oven, at the outlet from the US cell and inside the tank. Volumes of reaction compartments and delivery rates (200 ml/min) are so matched that the incoming fluid spends about one minute in each, during which time about 5% of the tank content (ca. 4,000 ml) is processed. On a statistical basis this means that, for 90% of the mixture to be processed for about 4-5 minutes, the system should be run for 2 h. This flow system has been patented and is mainly used for the treatment of polluted water by Fenton oxidation[41].

1 – Tank
2 – Centrifugal Pump
3 – Recirculation for Mixing
4 – Cooling Coil
5 – Regulation of Inlet to US Cell
6 – US Reaction Cell
7/8 – 300 kHz / 20 kHz Probes
9 – Peristaltic Pump
10/11 – MW Oven / Reaction Coil
12 – Refrigeration Oil from Coaxial Hose
13 – Cooling Oil
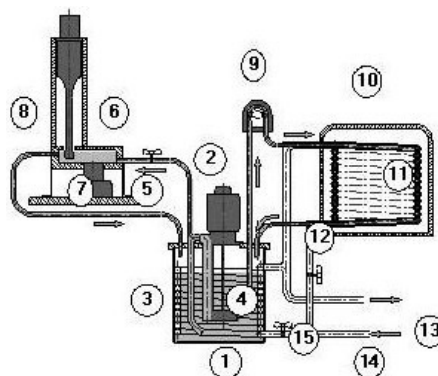14/15 – Valves that regulate the flow of cooling oil

Figure 6. A 5-liter prototype US/MW stop-flow reactor.

In recent years advanced oxidation processes (AOPs) have emerged as powerful methods for converting organic pollutants to non-toxic degradation products. They are based on the reactivity in aqueous solution of free radicals, especially hydroxyl radicals. AOPs are strongly promoted by US and MW and their combined irradiation showed a synergic effect.[40] We compared energy consumption for the combined US/MW treatment and for a simple thermal treatment, each one being carried out long enough to achieve 80% degradation of model compounds (i.e. 2,4-dibromophenol). With our prototype this took 70 min, while it required 6 h heating at 80°C. The US/MW system absorbs a total of 1900W (1100W as power consumption for the MW oven, 90 W for the 20 kHz US, 120 W for the 300 kHz US, 90 W for the pumps and 500 W for the cooling system). A 70 min treatment will then require 7980 kJ. A heating mantle absorbs 800W during the time required to heat the reaction mixture to 80°C; as this takes 35 min, the energy consumption amounts to 1680 kJ. To maintain the same temperature the electric mantle absorbs 150 W; therefore for a 5.5 h treatment another 2970 kJ must be added to the previous value, adding up to a total of 4650 kJ. Although the US/MW system appears to be more energy consuming, from our estimate the scale-up of the prototype (now in progress) will achieve an optimization (particularly of the MW generator and the cooling system), that will entail an energy saving of about 20-25%.

The latest improvement in our flow reactors was the introduction of tubing loops containing supported catalysts or reagents. For this purpose we employed tubes made of Teflon® and Kevlar® (Ø 2-7 mm, 20-70 cm length) or Pyrex® (Ø 10 mm, 20-40 cm length). In particular the latter, when filled with a mixture of inert material (Füller earth or sand) (particles Ø 0.05-0.2 mm), Pd/C (0.9% w/w) and Cs_2CO_3/K_2CO_3 1/1 (1.0% w/w) was used for Heck reactions. Although best results were achieved when the loop was inserted in the MW oven, good yields were also obtained using conventional heating. The following table resumes the results of Pd/C-catalyzed (1.5 mol %) Heck reactions obtained under different techniques using 4-iodoanisole (1 mmol) and the styrene (1.5 mmol) at 120°C, under Ar in the presence of Cs_2CO_3/K_2CO_3 (1 mmol each) in DMA.

	Power (Watt)	time (h)	conversion (%)	yield (%)
Oil bath, stirring	820[a]	10	90	74
US 20.5 kHz, combined heating in oil bath for 15 min	100	2	67	52
MW (open vessel)	100	1	100	88
Simultaneous US/MW	50/60	1	100	99
Sequential US/MW, stop-flow system with peristaltic pump	50/60	1	79	67
Stop-flow reactor[b] with column in conventional oven	960[a]	2	100	52 32[c]
Stop-flow reactor[b] with column in MW-oven	100	1	100	89 6[c]

[a] Nominal power
[b] Pd/C as stationary phase dispersed with 4-iodoanisole and the styrene inert material in the column.
[c] C-C homocoupling of 4-iodoanisole

Table 1. Pd/C-catalyzed Heck coupling under different techniques.

Simultaneous MW/US irradiation and the stop-flow MW reactor with a Pyrex® column filled with Pd/C, Cs_2CO_3/K_2CO_3 and inert material, gave the best results with shorter reaction times and higher yields. While in the former the temperature in the reaction vessel was strictly controlled, in the latter we could only measure the temperature after the column outlet, outside the oven. Although the bulk temperature was kept constant we suppose localized superheating in the column due to the MW-adsorbent properties of charcoal.

An additional advantage of these multi-units flow reactors is that they make it possible for individual reactions to be linked into multi-step sequences, so that one reaction seamlessly merges into another. In this way a fast route is created toward the final target, as a series of synthetic steps is turned into a continuous process. By varying flow rates, reaction media, temperatures, US and MW power, we can optimize reaction outputs. The time savings achieved by this flow-through method compared to conventional ones are really impressive.

CONCLUSION

Compared to standard batch techniques, our modular stop-flow and semi-continuous flow reactors stand out for their greater efficiency and flexibility, as they fit to each synthetic process the promoting effect of US, MW or combination thereof. The dramatic dispersing effect of US allows reactions to be carried out in media that are not solvents; this is advantageous because such heterogeneous reactions are usually much cleaner and a simple filtration suffices for the recovery of products. In some cases the use of supported catalysts or reagents entrapped in tubing loops offers the possibility of recycling the immobilized materials without resorting to any filtration/purification. The avoidance of stirring or shaking greatly reduces the mechanical degradation of the catalyst, so that it retains its activity for longer times. Our studies confirmed that high-throughput applications definitively require flow systems.

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