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ORIGINAL ARTICLE

MICROREACTOR TECHNOLOGY IN WARFARE AGENT CHEMISTRY*

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Summary

Even though the use of microreactors for synthesising classical chemical warfare agents or other compounds scheduled in the CWC (Chemical Weapons Convention) has not been published to date, the new technology has attracted the attention of the organic chemistry group of SPIEZ LABORATORY. Studies of the group show that in a few areas and sectors of chemistry, microreactors can provide a good alternative to the batch procedure. In classic warfare chemistry however, the technology can bring no benefits, since many reactions pro-duce a solid and are thus entirely unsuitable for microreactors.

Key words: Microreactor Technology; Microreactor-Systems; Warfare Agents; CWC

MICROREACTOR-SYTEMS

Round bottom glass flasks have always been used in organic chemistry for con-ducting reactions. Processes ranging from one milligram to several grams and reactive volumes from less than one milli-litre to several litres are absolutely common. Much time and energy is spent in searching for the best reaction parame-ters. Later, further problems arise during up-scaling, requiring further refinement and adjustment of the reaction parameters. Because of these recurring prob-lems, micro structured continuous flow reactors have experienced fast-paced development since the 1990s [1]. These reactors consist of minute channels em-bedded in a flat body of material (chip, Fig. 1) or of shaped ducts (Fig. 2) such as tubes of chemically resistant material. Glass, PTFE (Teflon), stainless steel or Hastelloy is used most frequently.

The minute dimensions of the channels in the range of 10 – 1000 µm form an ex-tremely large surface to volume ratio from which chemical reactions benefit due to optimum heat exchange and good mixing. The rapid heat exchange and efficient mixing greatly enhance the pro-cess, which often results in better selec-tivity, yield and purity [2]. The system particularly brings advantages when syn-thesising instable or highly reactive (ex-plosive) compounds as the product can on the one hand be processed further after formation and, on the other, always only small amounts are present in the reactor for a short time.

For about ten years now, microreactors have been commercially obtainable in a variety of forms. Specialised firms even manufacture reactors to order. But apart from reactors entire systems can also be purchased as compact devices (Fig. 3).

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* This topic was presented at the Australia Group Plenary (NETTEM Meeting) in Paris June 2012.

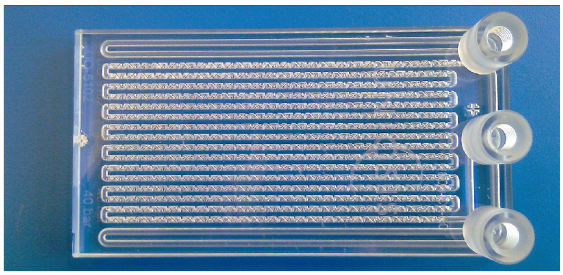


Figure. 1. Glass mixer chip.

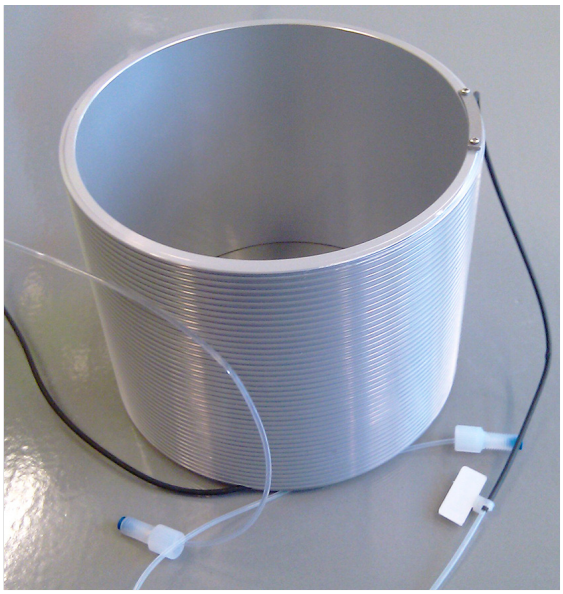


Figure. 2. Teflon coil reactor Uniqsis.

Along with the necessary pumps they also contain heatable holders for the reactors, fraction collectors and pressure systems for conducting reactions above the boiling point of the solvents used, similar to the microwave system. In most cases the devices are computer controlled so that a reaction sequence can be carried out under various parameters (optimising the reaction). Continuously, new peripheral equipment is being added to the market such as liquid handlers or diagnosis programs.

What is known as flow chemistry has also found its way into industry. Here the advantages of smaller dimensions as opposed to batch processes are espe-cially to be made use of. In implementing this technology from laboratory dimension to major dimension scaling-up (en-largement of the microreactors) is pre-ferred over scaling-out (microreactors in parallel). Because of this and due to its supposedly novel capabilities this new technology has been discussed in inter-national export control forums (Australia Group, Scientific Advisory Board of the OPCW). For this reason microreactor technology attracted also the attention of SPIEZ LABORATORY, although the use of microreactors for synthesising classical chemical warfare agents or other compounds scheduled in the CWC (Chemical Weapons Convention) has not been published to date.

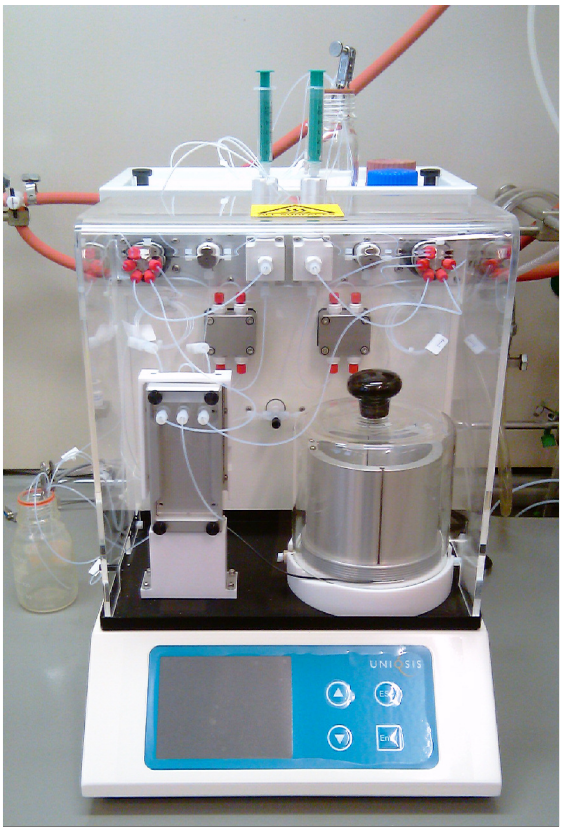


Figure. 3. FlowSyn™ Uniqsis.

STATISTICS

Often new technologies are praised as the solution to all problems. That was the case when microwave technology was introduced and it is now similar with mi-croreactor technology. Since 1950, mi-crowave technology is used for organic synthesis and has doubtlessly brought advantages in many areas. But it has not revolutionised organic chemistry. A com-parison of the publications and patents of both subjects should reveal the overall picture.

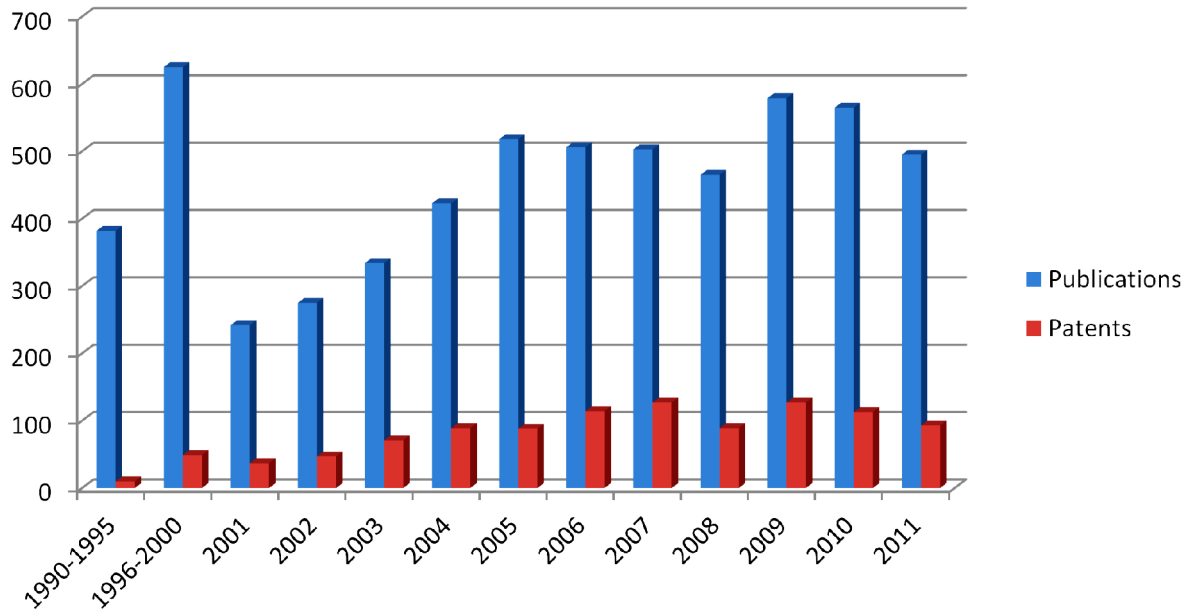


Figure 4. Number of publications and patents relating to microreactors (2001 until today and 5-year summary 1990 – 2000). Source: SciFinder, full text search «microreactor» on 14. February 2012.

Figure 4 shows that the number of scien-tific publications relating to micro-reactors has continuously grown over the last ten years until 2005 and from then on has remained at a relatively stable, more modest level. The number of patents shows a similar development. In contrast, the already well known microwave technology is the object of a multitude of publications and patents (Figure 5), whose number is still increasing [3].

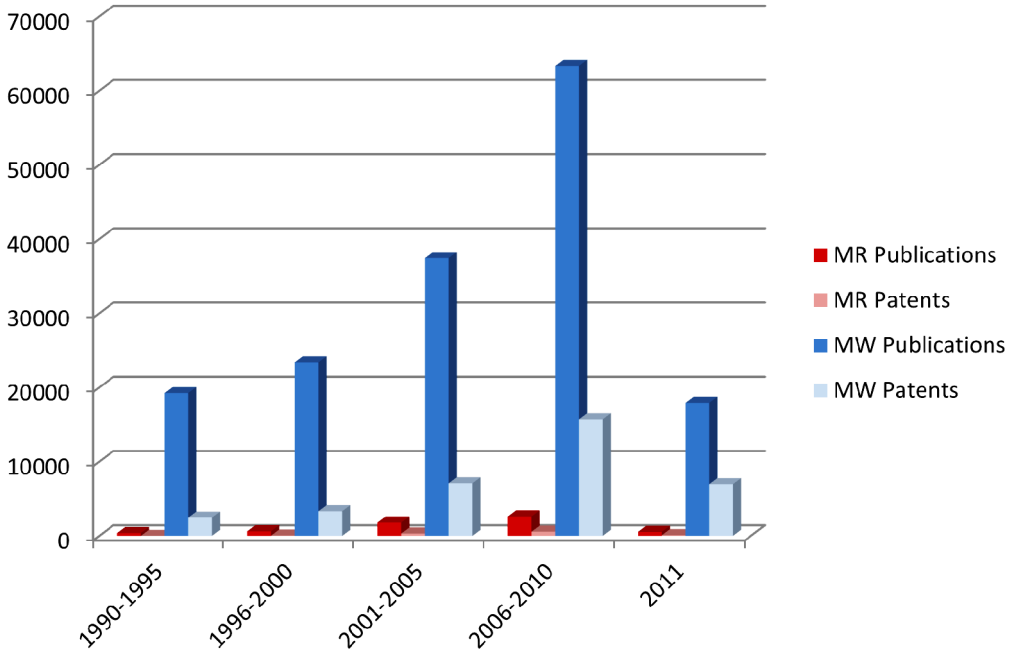


Figure 5. Comparison of number of publications and patents relating to microwave and microreactor technology. Source: SciFinder, full text search «microwave» (MW) and «microreactor» (MR) on 14 February 2012.

A second theoretical approach for cate-gorising microreactor technology regarding usability for the synthesis of chemical warfare agents and related compounds can be made with the help of an evaluation of the standard batch dedicated syn-theses used by the organic chemistry group of SPIEZ LABORATORY. Stand-ard procedures are grouped according to the following criteria gleaned from literature (for an overview see [4]) and their suitability for microreactors is eval-uated.

- Reactions that function fairly well with batch processing, but have a reaction time of >60 min combined with a reaction temperature of 100 °C or more, can be carried out with the microreactor system with difficulty only or not at all.
- Reactions that produce solids during synthesis cannot be carried out with microreactor technology. Precipita-tions cause blockage of the system and immediate termination of the re-action process.

On the basis of analysis of 81 different reactions relating to warfare agent chem-istry such as esterification, chlorination, fluorination, cyanidation, sulphuration, amidation, hydrolysis and oxidation, the standard batch dedicated processes of SPIEZ LABORATORY were rated as compatible or incompatible with micro-reactors (Figure 6).

So, after applying the selected criteria, microreactor technology can only be applied to 25 % of the standard reaction procedures used by our organic chemistry group. 75 %, of which 66 % due to solids and 9 % due to bad kinetics, are incom-patible with microreactor technology. A similar result has been published [5]. Thus, after evaluating 86 different industrial processes, the Lonza Company in Visp came to the conclusion that 63 % of these processes could not be carried out with microreactor technology.

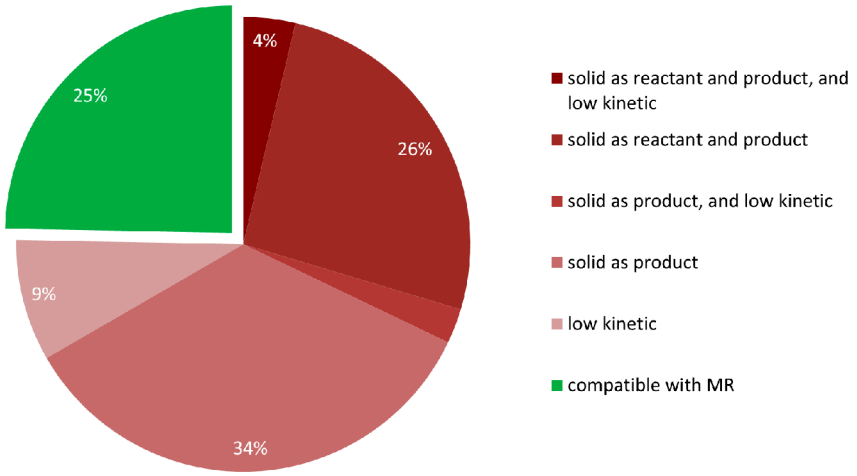


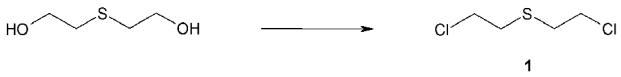
Figure 6. Evaluation of 81 batch methods routinely used in chemical warfare chemistry by the SPIEZ LABOR-ATORY regarding the suitability for microreactor technology. The percentage of microreactor compatible fireactions is shown in green (25 %), that of incompatible reactions in red (75 %).

APPLICATION EXAMPLES

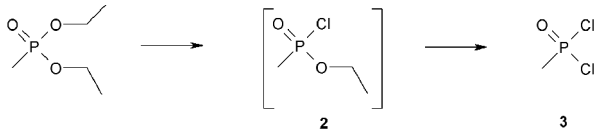
The examples of bis(2-chloroethyl)sul-fide (**1**), methylphosphonic dichloride (**3**) and bis(2-chloroethyl)(ethyl)ammonium chloride (**4**) synthesis (Scheme 1, 2, 3) clearly show that microreactor technology is unsuitable for reactions that produce solids or reactions with bad kinetics.

Bis(2-chloroethyl)sulfide (**1**) can be syn-thesised according to conventional batch methods with a yield of 95 % and a GC/MS purity of 99 % without difficulty and relatively fast (Scheme 1). After a reaction time of 1 h with a 350 ml stand-ard lab sulfonation flask, the amount ob-tained is about 30 g.

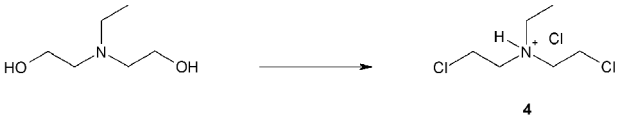
The same reaction and method also works very well in a microreactor system. With a yield of 92 % and a GC/MS purity of 97 %, the values obtained are practical-ly equally good as with the conventional batch procedure.



Scheme 1. Synthesis of bis(2-chloroethyl)sulfide (**1**).



Scheme 2. Synthesis of methylphosphonic dichloride (**3**).



Scheme 3. Synthesis of bis(2-chloroethyl) (ethyl)ammonium chloride (**4**).

For synthesising methylphosphonic di-chloride (**3**) the two ester groups are substituted with one chlorine atom each in two subsequent steps, but without isolating the intermediary product **2** (Scheme 2). From the kinetic point of view (approx. 15 min), the first step does not provide a great obstacle for the batch process. For the second step to the end product **3**, however, considerably more energy has to be invested. In the batch process 105 °C are required for 3 h. A yield of 80 % and a ^{31}P-NMR purity of 98 % can be achieved with this method.

In a microreactor system the first step is achieved to 96 % within a retention time of 4 min and at a temperature of 100 °C. But the second step could never be fully accomplished. In the best case only 35 % of the end product **3** could be detected.

Bis(2-chloroethyl)(ethyl)ammonium chlo-ride (**4**) can be obtained with the batch method after 2 h with a 87 % yield and a ^{1}H-NMR purity of >95 % (Scheme 3). This product always appears in the form of a hydrochloride salt.

Efforts to synthesise bis(2-chloroethyl)-(ethyl)ammonium chloride (**4**) according to this method in a microreactor system were unsuccessful. After less than 20 sec., the ensuing hydrochloride salt **4** precipitated, blocking the reactor. An immediate increase in pressure resulted and the device shut off automatically.

CONCLUSION

Microreactor technology is currently re-garded as promising new technology with a broad range of possible applications in organic chemistry. However, our experi-ence shows that this technology, like many others, cannot solve all problems. Certainly, in a few areas and sectors of chemistry microreactor technology will provide a good or even better alternative to the batch procedure. In classic warfare chemistry, however, it can bring no benefits when compared to the conventional batch procedure, as many reactions produce a solid, the main criterion excluding microreactor technology. Furthermore, an individual setup has to be developed for practically every batch procedure that is to be replaced with microreactor tech-nology, requiring much effort and time.

Of course it must not be forgotten that new developments in this technology could make it possible to conduct further reactions with this system.

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