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Miniaturized Reactors -- Review

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Abstract

Miniaturized reactors are becoming a new market share in the near future because the reactors show many advantages (e.g. small size, high surface-to-volume, safety). This article reports review and challenge in research and development (R&D) of the miniaturized reactor; moreover, areas of implementations are also included. To date, R&D has focused on production in high mass, comprehension in fluid flow dynamic, integration of analytic devices, and cure for clogging problem as well as the implementations of the reactor have early been applied into chemical, pharmaceutical, biomedical, and also microelectronic productions.

Keywords: Microchannel; Microfluid; Microreactor; Miniaturized reactor;

I. Introduction

Miniaturized reactors are a new one micro- and nanotechnology. Miniaturization is defined as the process of making something very small using modern technology so the miniaturized reactor should mean the reactor that is processed by the miniaturized process – MEMS, lithography, laser, etc. – into very small dimension (e. g. micro- or nanometers). Many words related to miniaturized reactor such as microreactor, lab-on-a-chip, and miniaturized total analysis system (μTAS), all of them are subset of miniaturized technology. Moreover, there are also many devices that fabricated by miniaturized technology (e.g. microfluidic, microchannel, micromixer, and microheat exchanger).

Because many of its advantages, the miniaturized reactor are now becoming a new production processes. Although, the miniaturized technology is still at the early stage but many advantages of it, such as its small size, high surface-to-volume ratio, and safety (Fig. 1), are a driving force to increase a new market share. The companies that implement today's technology may not break even now but they are expected that they will profit in the future's process. (Pieters et al., 2006; and Wille and Pfirmann, 2004) Therefore, miniaturized reactor is the highlight technology that has been applying for wide application areas.

There are various applications of miniaturized reactors presented in many articles but there is lack of an account report that reported the applications of the reactors in many fields. The main goal of this article is to review and challenge the implementation of miniaturized technology. What areas, when, and why to select this technology for implementing are accounted that, hopefully, will be useful for end users for deciding in the future. This report is started with the miniaturized fabrication technology and then the kinetic reaction study in the reactor is addressed. Next, the heat transfer and fluid flow in the microchannels are described and compared with the macrochannels. In addition, the main research groups and the main commercial manufacturers are also included. Following by some implementations of this technology in many application fields are represented. Finally, the integrated measurement and control devices into the reactor are reviewed.

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ADVANTAGES

Small size
- requiring less space
- consuming small energy and material
- short resident time

High surface-to-volume ratio
- often increasing conversion
- reducing hot spot problem
- high rate of heat transfer

Safety
- consuming small reagents
- easy to control
- environment friendly

Economic
- low-cost

DISADVANTAGES

Short life time
- clogging problems

Low mass production

Figure 1. Advantages and disadvantage of miniaturized reactor. (Ehrfeld et al., 2000)

II. MINIATURIZED REACTOR ENGINEERING

A simple miniaturized reactor assembly composes of the smallest parallel channels called microstructures. The arrays of microstructures (elements) are connected to the external line of fluid and putted on the base are called units. (Ehrfeld et al., 2000) Fig. 2 represents one type of miniaturized reactor assembly. There are many methods for fabricating miniaturized reactors; however, lithography is the main method for invention. The lithography is originally from photo printing process on the smooth surface that was invented in 1798. At the present, Ehrfeld's group borrows the deep lithographic method and combines with electroforming and molding processes (called LIGA process) for miniaturized fabrication. (Ehrfeld et al., 2000) In the first step of fabricating, a master form is transferred into a resist layer on an electrically conductive substrate and then the precise microstructures can be generated by deep X-ray lithography. In the next step, the microstructures are continuously transferred into electroforming to construct complementary structures. In some cases, these microstructures are the final products; however, they can continuously be used as the master tools for a replication process. (Ehrfeld, 2002) The lithographic process is the general basis for other methods to fabricate miniaturized devices.

Microelectromechanical systems (MEMS) (also called micro systems technology – MST) refer to microscopic devices integrated with electrical and mechanical components and, originally, are used for constructing electronic circuits. It is the system fabricated by lithographic method. However, not only lithography, MEMS can also be fabricated from such other methods; decomposition processes, photo-lithography, and etching processes. As its advantage, MEMS can be implemented to various materials, such as glass, ceramic, silicon, and etc. but the silicon is the most common for fabrications because originally, they were used in microelectronic manufactures. (Hynes et al., 1999 and Jensen, 2006) Jensen's group, one main research group at MIT, has implemented deep reactive ion etching (DRIE) process for fabricating miniaturized reactors. (Jensen, 2000) MEMS, now, have been challenged for implementing in broad fields of micro-engineering for mechanical, electrical, chemical, and also including biomedical engineering. Further

fabrication of miniaturized reactor could also be found in Suryawanshi et al. (2018) as well as Boonkhao et al. (2013).

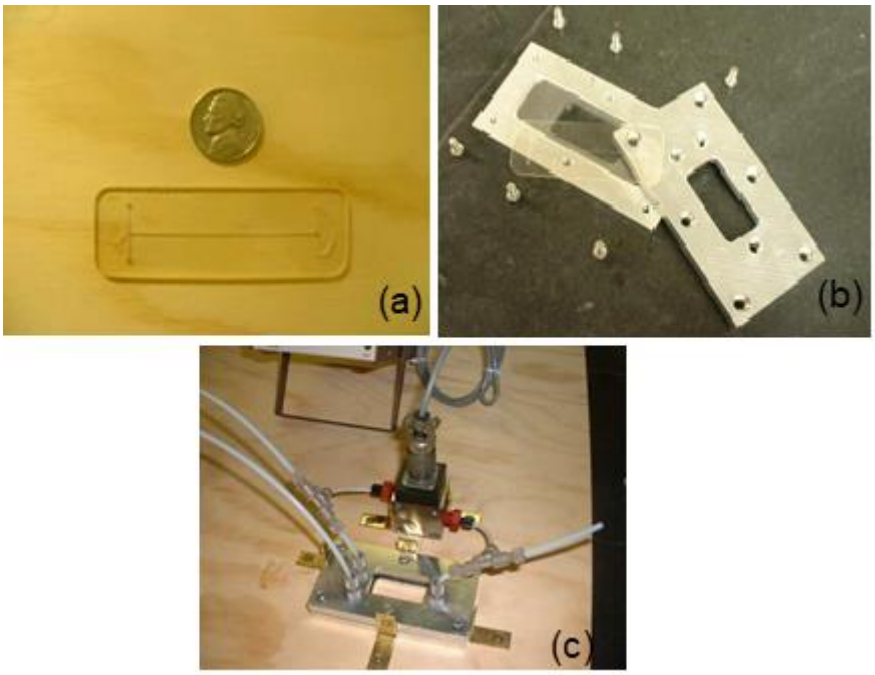

Figure 2. Miniaturized reactor assemblies (a) microchannel (microstructure) (b) microchannel and based unit (c) completed integrating miniaturized reactor. (Source figure: http://www.stevens.edu/engineering/cbme/UG/sdp/spring02/microchannel/wafer.html)

The implementation of miniaturized reactor as a paradigm of chemical kinetic study is the advantage because many parameters can be studied, measured, and operated in the reactor to be prototypes before applying to pilot or industrial scale by low cost and low risk. For examples, Burn and Ramshaw (1999) and Dummann et al. (2003) studied nitration reaction that is highly exothermic reaction in microreactor. The results showed that the increasing flow velocity gave the increasing in nitration conversion; moreover, Antes et al. (2003) addressed that to improve strong exothermic sensitivity, analytical techniques are required. Steinfeldt et al. (2003) compared the measurement kinetic data between packed bed reactor and the microreactor coated with catalyst inside channels, the microreactor showed the good catalytic results than the packed-bed reactor in high reaction temperature. Walter et al. (2005) studied mass transfer limitation in microreactors and proposed the criteria to consider where mass or kinetic limitation region is. Abdallah et al. (2006) could measure the K_La coefficient of very fast hydrogenation reaction in the mesh microreactor, the result model could be predicted with the CFD simulation. Kerby et al. (2006) evaluated the different relation between mass transfer and efficiencies of an enzyme reaction. To date, most of researches have attracted on gas and liquid phase reactions covering catalysis reaction, gas-liquid-solid reactions. (Haswell and Skelton, 2000; Doku et al., 2005; and Geyer et al., 2006) There have been many affords to deposit catalyst inside the microchannels. (Heule et al., 2003; Wan et al., 2003; Kiwi-Minster and Renken, 2005; Younes-Metzler et al., 2005; and Meille, 2006)

In addition, the study of exothermic reaction can also be applied to the reactor because it has high surface-to-volume ratio so the heat transfer rate is very high and then the hot spot problems will be boiled down. The kinetic reaction of ammonia oxidation, for instance, could be reliable in the explosive region in the microstructure reactor. (Rebrov et al., 2003) Moreover, the performance of heat transfer in the microreactor showed better when compared with the packed bed reactor.

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(Steinfeldt et al., 2003 and Tadd et al., 2005) However, although the heat transfer rate of microreactors shows excellent, it has still needed more inventions in heat managements, such as integrated heat control device.

Fluid flow in the reactor is one important that affects the reactor performance because the reactor is narrow in dimension so the fluid properties are scaled that relate and different with the macroscopic fluid. (Janasek et al., 2006) The fluid flow (include mixing) in the cross dimension (or radial dimension) can be accomplished through the diffusion. At this scale diffusion provides a driver for both rapid and controlled mixing of fluids (see Figure 3). (deMello, 2006) For flow through the reactor, electro-osmotic flow (EOF) can be used as a pumping technique by no need the external pump. (Kohlheyer et al., 2005 and Geyer et al., 2006) Nikbin and Watts (2004) also demonstrated that EOF, a useful characteristic, could be used to move the reagent over a solid-supported catalyst bed as in comparison with pressure driver systems were found to be highly irreproducible. However, fluids characteristics have still not clearly understood in this scale; therefore, fluid flow researching in miniaturized reactor are required and also associated with other helpful methods such as integrated sensor/actuator devices, CFD simulation, flow pattern maps, and etc.

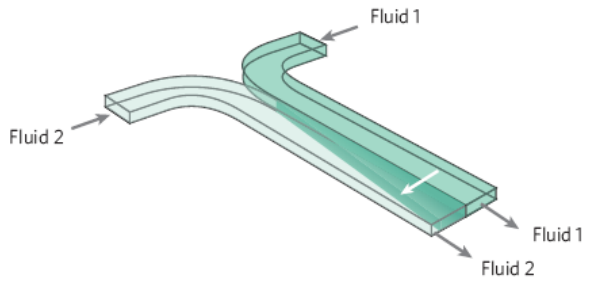

Figure 3. Diffusion of fluid through the microchannel (deMello, 2006)

Because of its low mass production, miniaturized reactors are suitable for the small-scale productions. Although, the reactors give the high conversion but their productions are still in small amount of compounds because of its dimension in micro- or nanometers. However, replication of the reactor units in parallel is one strategy for producing a lot of mass production. (Jensen, 2001) The scale-out should be considered with economy, safety, and product demands. (Watts and Haswell, 2005) Therefore, the challenge in high mass production in miniaturized reactor has still required.

Although, miniaturized reactors have many advantages but they also have disadvantages and problems for implementing. The reactor consumes small amount of energy while implementing whereas in the production of stainless steel miniaturized reactors but, fortunately, Kralisch and Kreisel (2007) presented that LCA assessment of the reactor was good ecology sustainable. Other problem still researching is the clogging problem that induces the reactor has short lifetime. However, Poe et al. (2006) reported the method for solving clogging problem by performing the reaction in a mono-disperse droplet flow, the solid particles are isolated from the walls of the reactor, but this method is only for specifically reaction. Therefore, in case of handle solid it has still required the diversity of synthesis ways to solve this problem.

Miniaturized reactors, to date, still are in the early stage; therefore, many research areas have been required to force this technology into the new market. Table 1 presents the main research groups that have been researching in this technology. From the comprehensive review, it is shown that, at the present time, the miniaturized technology are almost inventing on the biochemical and

biomedical areas ((3) – (16)). Research group (1) and (2) are the main groups in microfabrication,

Table 1. Main research groups in miniaturized technology

Research groups	Research areas	References
(1) Ehrfeld research group, Institute für Mikrotechnik Mainz GmbH, Germany	Chemistry and pharmacy, Energy technology, Analytic and diagnostics, Sample preparation, Simulation, Membrane technology, MEMS[(a)] vacuum component, and Instrument development	http://www.imm-mainz.de/seiten/en/index.php
(2) Jensen research group, MIT	Microsystems for chemical and biological applications, Microchemical systems, Microchemical systems for power generation, µFermentors, and BioInfoMicro	http://web.mit.edu/jensenlab/
(3) Haswell research group, University of Hull	Microreactor for atom efficient synthesis, Microwave assistance for chemical synthesis. Microfluidic sorting , processing and analysis of viable cells, DNA characterisation, and Synthesis and nanotechnological applications of tethered silicates.	http://www.hull.ac.uk/chemistry/academic_staff.php?id=sjh
(4) Watt research group, University of Hull	Organic chemistry and electrosynthesis in micro reactors, and On-chip analysis of reaction mixtures	http://www.hull.ac.uk/chemistry/academic_staff.php?id=pw
(5) Landers Bioanalytical Chemistry Research Group, University of Virginia	DNA/Genetic analysis, Protein peptide analysis, and Small molecule analysis	http://faculty.virginia.edu/landers/
(6) Wheeler Lab-on-a-chip Group, University of Toronto, Canada	Rapid prototyping of DMF devices,[(b)] Integrated proteome profiling, Cell-based assays, Microgel flows, and Shear stress in the aortic valve	http://www.chem.utoronto.ca/staff/WHEELER/
(7) MicroSystems and BioMEMS Lab, University of Cincinnati	Disposable BioChips / BioMEMS,[(c)] Microfluidics Devices & Systems, Plastic Materials & Micromachining, Optical MEMS, Magnetic MEMS-Actuators/Sensors, and Integrated Microsystems	http://www.biomems.uc.edu/
(8) Institute of Analytical Sciences (ISAS), Dortmund and Berlin, Germany	Plasma discharge, Separation technique, and Cell manipulation	http://www.isas.de/english/menu-top/home/
(9) Harrison, J. D. research group, University of Alberta, Canada	Microfluidics, Proteomic, Multiplexed devices, and Bead based systems	http://www.chem.ualberta.ca/~harrison/
(10) Mathies, R. A. research group, University of California, Berkley	DNA sequencers, DNA genotypers, Extraterrestrial analysis, DNA-based computing, PCR on a chips, Cell interphasing, and Pathogen detection	http://www.cchem.berkeley.edu/ramgrp/alpha/
(11) Belder research group, University of Regenberg, Germany	Microfluidics, High throughput screening, Capillary electrophoresis, and Surface chemistry	http://www-analytik.chemie.uni-regensburg.de/belder/index_en.htm

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Table 1. Main research groups in miniaturized technology (cont'd)

Research groups	Research areas	References
(12) Microsystem Technology Lab, Royal Institute of Technology (Kungliga Tekniska högskolan, KTH), Sweden	MEMS, MedMEMS, (d) BioMEMS, OptoMEMS,(e) and RFMEMS(f)	http://www.s3.kth.se/mst/
(13) Biosensor Lab, University of Arizona	Lab-on-a-Chip, Protein Nanoarray for Single Molecule Detection (SMD), CFD Modeling for Greenhouses, and Blood Coagulation Monitoring with Quartz Crystal Microbalance	http://biosensors.abe.arizona.edu/index.html
(14) Biofunctionalized NEMS Laboratory, The Pennsylvania State University	Molecular mechanics, Bio-NEMS, Micro/Nano Manufacturing, and Micro/Nano Fluidics	http://www.esm.psu.edu/huang/
(15) BIOS Lab-on-a-chip Group, University of Twente, The Netherlands	Micro- and nanofluidics, Analysis system and sensor, and BioMEMS	http://bios.ewi.utwente.nl/
(16) Department of Micro and Nanotechnology, Technical University of Denmark (DTU), Denmark	MEMS, Bio/Chemical Microsystems, and Nanosystem Engineering	http://www.mic.dtu.dk/English.aspx
(17) Bioanalytical Microsystem & Biosensor Lab, Cornell University	Engineered devices for detection hazardous chemical in environmental, food, and medical diagnostics.	http://hive.bee.cornell.edu/bmb_lab/index.html
(18) Craighead, H. G. research group, Cornell Univeristy	NEMS,(g) Single molecule studies, Biosensor, microfluidics and chemical analysis, and Nanofabrication, nanomaterial, nano optic and electron transport	http://www.hgc.cornell.edu/index.html
(19) Advance Micro-/Nano- Devices Laboratory, University of Waterloo, Canada	MEMS/NEMS, Microassembly, and Nanodevices for biomedical applications	http://biomems.uwaterloo.ca/index.html
(20) MaDevitt research laboratory, University of Texas at Austin	Lab-on-a-chip sensors	http://www.tastechip.com/index.html
(21) Kitamori Laboratory, Department of Applied Chemistry, School of Engineering, The University of Tokyo, Japan	Integrated Chemistry Lab, Lab-on-a-Chip, Micro chemistry system, Microchip, Microfluidics, and Thermal Lens Microscope	http://www.chem.t.u-tokyo.ac.jp/appchem/labs/kitamori/top_e.htm

Remark: (a) MEMS – microelectromechanical systems, (b) DMF – digital microfluidic, (c) BioMEMS – biomedical application for MEMS, (d) MedMEMS – medical microelectromechanocal systems, (e) OptoMEMS – optical components for MEMS, (f) RFMRMS – radio frequency signal components for MEMS, (g) NEMS – nanoelectromechanical systems

for (1) in LIGA processes and (2) in MEMS. Group (17) focuses on the environmental impact and the rest groups are in the integrated microdevices. Table 2 shows the list of commercial manufactures of miniaturization technology.

III. CHEMICAL AND BIOLOGICAL APPLICATIONS

The miniaturized technology is exactly not suitable for all productions so what areas are

becoming for this technology? Watts et al. (2003) proposed the impact consideration for using this technology; the chemical compatibility, the ease and reproducibility of fabrication, material support with the solvent of interest, and compatibility with detection methods. Moreover, Whitesides (2006) also addressed the choosing and focusing on initial applications and developing strategies to complete the cycle of development. Below are some examples of the areas that are becoming for applying this technology.

Cell Culture

Miniaturized devices are suitable for cellular applications because the scale of the devices is close to the cellular level. (Walker et al., 2004) Cell cultivation could be performed in parallelized fluid segments that were formed as droplets at a channel junction where organic and cell containing aqueous phase were merged (Martin et al., 2003) and also could be measured cellular activity, for example, by combined MEMS technology and liquid phase photolithography to create microfluidic chips. (Pearce et al., 2005)

Cell based microdevices are a lot of advantages for health science. For examples, the whole cell can be made as the biosensor, as genetic analysis system, as stem cell culture, and etc. (El-Ali et at., 2006) The integrating device to cell based microdevices can also explore the new discover for biomedical and biopharmaceutical technology.

Table 2. List of commercial manufactures

Commercial manufactures	Description of the manufactures	References
Ehrfeld Mikrotechnik BTS	The company is located in Germany. There are many devices that can be found here, mixers, reactors, heat exchangers, sensors/actuators, connectors, clamping devices, building sets, and high-flowrate.	http://www.ehrfeld-shop.biz/shop/catalog/index.php
Micronit	Micronit is based on the Netherlands. Microfluidic devices are the major products.	http://www.micronit.com
Micro-Reactor Systems Provider	The company has three branches in USA, UK, and Japan. The main products, microfluidic devices, are sold with the license of Acclavis for fine and special chemical production.	http://www.mrsp.net
CPC-Systems GmbH	CYTOS Microreactors are the major product of the company that is located in Germany.	http://www.cpc-net.com
Systanix	The company is based in USA and co-researched with Cornell University. Microreactors for pharmaceutical synthesis are the main products.	http://www.systanix.com
Microinnova	Microinnova is placed in Austria. The company researches in many filed of microchemical engineering, including microreactors.	http://www.microinnova.com
Syrris	Syrris is located in UK and USA. The products are composed of flow chemistry, microreactors, and automation technology that implement for pharmaceutical, petrochemical, environmental, and academic research.	http://www.syrris.com
The Dolomite Centre	The company is the partner of Syrris Company that provides the design and manufacture of microfluidic devices, instruments, and systems.	http://www.dolomite-centre.com

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Clinical Diagnostics.

The treatment examining between miniaturized reactors with the clinical pre-treatment can be performed before implementing to the patients. Ptolemy et al. (2005) investigated a new strategy to integrate sample pre-treatment with chemical analysis using on-line preconcentration with chemical derivatization by CE and UV detection. Seong et al. (2003) described a microanalytical method for determining enzyme kinetics using a continuous-flow microfluidic system. This approach provides a new means for rapid determination of enzyme kinetics in microfluidic systems, which may be useful for clinical diagnostics and drug discovery and screening. Guzman et al. (1997) reviewed the likely impact of the technology of CE and the role of it analyze concentrator-microreactor on the analysis of biomolecules, present on complex matrices, in a clinical laboratory.

Proteins

Proteins are an important part of life even DNA is also obtained from digestion and identification of proteins. The digestion process is used to cut large protein molecules to small molecules (peptides) and then the peptides are identified. Both of analytical processes can be associated by miniaturized reactors. The integrated CE to miniaturized reactors has favored way for improving digestion proteins (e.g. fast digestion, low protein concentration). The fast proteindigestion was investigated by preparing the monolithic microreactor in the fused-silica capillary by in situ polymerization of acrylamide, N-acryloxysoccinimide and ethylene dimethacrylate (Duan et al., 2006a, b, and c), the result promised to achieve from hours to minutes. Schoenherr et al. (2007) connected microreactor between two of CEs (CE-microreactor-CE). The intact protein samples were injected into the first CE to separate the samples, then the proteins were digested at the on-line microreactor, and, finally, the peptides were fragmentized and identified at the second CE. Ye et al. (2004) developed a nanoliter enzyme microreactor for on-line CE peptide mapping of proteins which was prepared by in situ polymerization of glycidyl methacrylate and ethylene dimethacrylate in a capillary. The microreactor allowed a small amount of protein (picolitre) sample to be digested and the overall analysis time was only in minutes. Moreover, the temperature is also the factor of digestion time, Sim et al. (2006) carried out a temperature-controllable microreactor to optimize the digestion time. The resulting peptide sequence coverage ranged was sufficient for practical protein identification. Most of the digestion processes are occurred in the microreactor or the CE but the identification processes are identified by the integrated devices.

Mass spectrometry (MS) is a common device to be integrated into the miniaturized reactors for protein identification. Zhao et al. (2006) fabricated fused-silica CE, as microreactor, connected to nano-electrospray MS for on-line digestion and fast peptide mass. This method showed generation of tryptic peptides with sequence coverage up to 90% within minutes and the immobilized enzyme could be cleaned easily, enabling the microreactor to be reused for nanoelectrospray. Gao et al. (2001) constructed a miniaturized membrane reactor integrated with either matrix-assisted laser desorption/ionization MS (MALDI-MS) or electrospray ionization MS (ESI-MS), the integrated device presented rapid and sensitive protein identifications. Craft et al. (2002) developed a procedure for protein identification using MS that incorporates sample cleanup, pre-concentration, and protein digestion in a single-stage system. The microcolumn digestion procedure represents the next step toward a system for fully automated protein analysis through capture and digestion of the adsorbed protein on hydrophobic surfaces. The application of miniaturized reactor to the protein has still required techniques for integrating all of analysis processes (digestion, separation, and identification) into the one device.

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Polymerase Chain Reactions (PCR)

The diagnostic to the PCR technique is very important because the PCR technique has many advantages in the DNA studies, for example, the detection of DNA of virus before any antibody response in the infected person (Zhang and Yeung, 1998) so much diagnostic research are presented herein. Chou et al., (2002) designed and fabricated the miniaturized cyclic PCR device in low-temp confined ceramics. Utsami et al. (2007) developed the microreactor with a single cell for PCR by using MEMS and also showed the successful amplification of the DNA by using the microreactor. Hofmann et al. (2004) scaled down a silicon microsystem as a miniaturized DNA-amplification device for performing PCR with reduced volumes of 7 μL. Krishnan et al. (2005) described the theoretical design of a microchip for the amplification, detection and counting of individual nucleic acid molecules in an ensemble of non-specific molecules. The theoretical accuracy of this technique is only limited by the Poisson statistics of sampling. Tripathi et al. (2005) proposed the method of multiple time scales with regular expansions is used to obtain the effective dispersity and the analytical results are compared with computational fluid dynamics simulations. Wang et al. (2005) reported a method capable of quantitative detection of low-abundance DNA/RNA molecules by associating with fluorescence spectroscopy, molecular beacons, and a molecular-confinement microfluidic reactor. The detection time is required less than 2 minutes to complete the detection. Sung et al. (2003) developed the microthermal cycler which showed excellent control performances and performs a successful PCR for DNA. Zhang and Yeung (1998) demonstrated an integrated on-line system with a fused-silica capillary as the microreactor for PCR and capillary gel electrophoresis with laser-induced fluorescence detection for DNA typing and disease diagnosis. In conclusion, PCR technique has still required the invention in fast PCR, automatic analysis device, and integrated device.

DNA Sequencing

The analysis of DNA sequencing can be identified by using miniaturized technology. Wang et al. (2006) reported on the use of a polymer-based continuous flow thermal cycler (CFTC) microchip which could be reused for subsequent sequencing runs (> 30). The CFTC microchip was subsequently coupled to a solid-phase reversible immobilization (SPRI) microchip for purification of the DNA sequencing ladders prior to gel electrophoresis. Tan and Yeung (1997) demonstrated an integrated on-line prototype for coupling a microreactor to CE for DNA sequencing. The system is compatible with highly efficient separations by a replaceable poly (ethylene oxide) polymer solution in uncoated capillary tubes. The implementation of identification technique to miniaturized reactor is main challenge in DNA sequencing because the analyzing sequence requires more technique in integrating analysis devices.

Combinatorial Syntheses

Because of fast reaction, high conversion, consuming small reagents, and safety (Box 1), the miniaturized reactor is appropriated to use in the chemical libraries' construction for combinatorial biosyntheses. (Watts and Haswell, 2005; Claus et al., 2001; Kobayashi et al., 2006; Ahmed-Omer et al., 2007; and Watts and Wiles, 2007)

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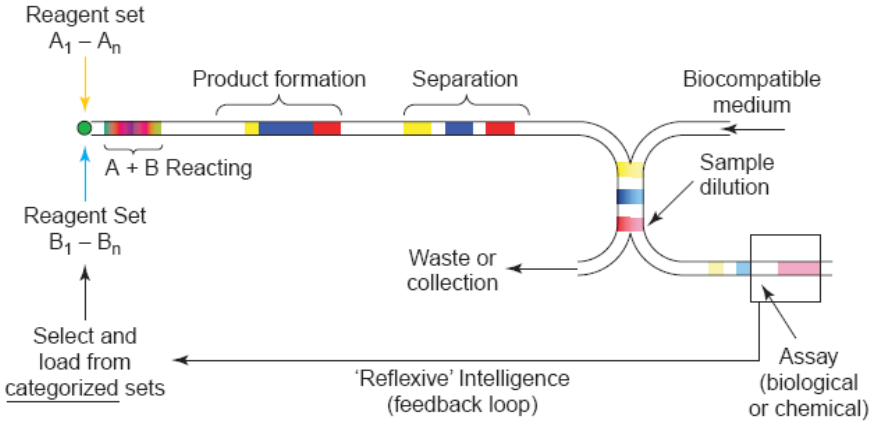

Figure 4. Sequential combinatorial syntheses integrating with assay. (Fletcher et al., 2002)

There are two modes of chemical syntheses, sequential and parallel syntheses. (Kikutani and Kitamori, 2004) The sequential syntheses in miniaturized reactors are more favorable than the parallel syntheses because while there are a lot of starting reagents, the microchannels are less required and less complex than the parallel syntheses. (Kikutani et al., 2005) Fig. 4 showed the sequential combinatorial syntheses integrating with assay. The reagent set A and B are injected into the microreactor and react along the microchannels, then the products separation by integrating device, HPLC or CE, and tested the assay at the end of the channels. (Fletcher et al., 2002) For example, a miniaturized-SYNthesis and Total Analysis System, called μSYNTAS, integrating with microprocessor and time-of-flight mass spectrometry (TOF-MS) was a successful sequential chemical libraries construction, as well as the parallel syntheses by Mitchell et al. (2001). A sub-reaction of "Ugi multicomponent condensation" was distributed into the μSYNTAS, the reaction was performed between the five piperidine derivatives and formaldehyde to produce five different iminium cations.

There are less of research for parallel syntheses because they require a lot of microchannels and are also complex for integrating all the microchannels into the miniaturized reactor. For example, the syntheses between number n reagents with number m reagents, the miniaturized reactor have to compose of n + m input channels and n × m output channels. Fig. 5 represented example for 2 × 2 parallel syntheses. For developing the parallel syntheses, Kikutani et al. (2005) fabricated continuous-flow chemical processing (CFCP) for parallel syntheses; it was integrated with the micro-unit operation (MOU). The advantages of this device are the integrated many operation devices into the reactor, e. g. microextraction. However, the application to this area has still required the combination and association with other technology, for example, Comer and Organ (2005) used microwave irradiator to assist in the synthesis, the result showed excellent conversion and seem to be no clogging problem.

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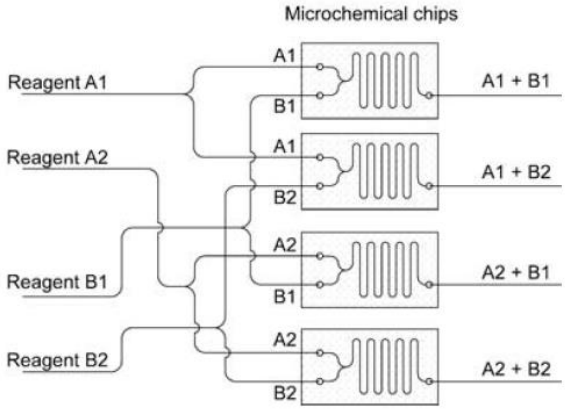

Figure 5. Parallel combinatorial syntheses for 2 × 2 starting reagents (Kikutani et al., 2005)

Fine Chemical and Pharmaceutical Production

Fine chemical and pharmaceutical drug syntheses require highly controlling many parameters while synthesizing; therefore, miniaturized reactor is the answer for this problem. (Edel et al., 2002) The miniaturized reactor can mitigate some controlled parameters which are important in bulk syntheses (e.g. temperature and pressure). For example, ultrafine particles of $CaCO_3$ were synthesized from $Ca(OH)_2/H_2O$ slurry in micropore-plate by controlling only slurry concentration, gas flow rate, and temperature. (Wu et al., 2007) The $CaCO_3$ crystalline is grown in only one type (calcite) from three types (calcite, aragonite, and vaterite). Moreover, Nagasawa and Mae (2006) and Nagasawa et al. (2007) studied experiments and model relation between size and distributions, and reaction conditions based on the hypothesis on fine-particle formation mechanism. The model studied will be useful as a guideline for industrial application.

Moreover, a batch synthesis for pharmaceutical production may be possibly replaced because the same reactions could be run continuously in the microreactors. (Wille and Pfirmann, 2004 and Kirschneck et al., 2005) Each of slug flow (droplet) in the microchannels is accounted as each batch and operated continuously (see Fig. 6). However, Roberge et al. (2005) argued that the microreactor will revolutionized the fine and the pharmaceutical processes if the microreactor capable to handle the solid synthesis and yield improvement compared to batch.

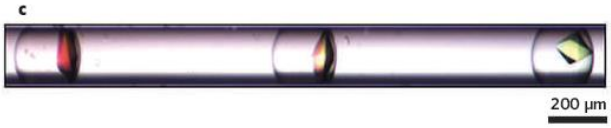

Figure 6. Crystallization process in the microchannels. Each of slug flow is one crystallization batch and this process is run continuously. (Whitesides, 2006)

Hazardous Chemical

The one important useful of miniaturized technology is the highly safe while implementing to hazardous and explosive processes because the operation volumes are very small, so the safety operations are also mitigated. (Zhang et al., 2004) Janicke et al. (2000) presented that the combination of microchannels with heat exchanger allowed dangerous mixtures of hydrogen and oxygen to be mixed and react safely in the Pt/Al_2O_3-coated microchannels. Ajmera et al. (2001) demonstrated the synthesis of hazardous (phosgene) and corrosive gases (chlorine) over the microfabricated packed-bed reactor. Zhang et al. (2004) investigated 70-mg scale reaction in microreactor between piperidone and diazo, that is highly exothermic and hazardous. DuPont is the

one commercial example that has produced many hazardous chemicals in microreactors (e.g. cyanides, peroxides, and azides). (Jensen, 2001)

In addition, the hazardous wastes from the productions could also be treated by miniaturized technology. Kulp et al. (2002) introduced CE in analysis of the degradation of hazardous phenols, which is easy to perform, cheaper, shorter time and higher efficiency in analysis while compared with HPLC and could be introduced to most laboratories. Meyer et al. (1999) examined that hydro-dechlorination reaction of 1, 3-dichloropropene, the waste stream from epichlorohydrin manufacturing, presented a good significant of the dechlorination on $Pt/\gamma\text{-}Al_2O_3$ and $Ni/SiO_2\text{-}Al_2O_3$ catalysts in a packed-bed microreactor.

There are wide areas to implement miniaturized reactors. However, in order to implement the reactor to the real production, measurements and controls are significantly required that is described in the next section.

VI. MEASUREMENT AND CONTROLS

The general consideration for using any measurement and analysis devices with the miniaturized reactors is what measured parameters are and how to measure these parameters. Generally, users already know which the parameters they want to measure since the remaining problem is how to measure these parameters. The integration of sensor or analysis devices into the reactors is favorable way to measure parameters; however, they are difficult to integrate the devices into them because the reactors are very small in the dimension. At the present, there are two common ways to integrate devices into the reactors; 1) fabricating the reactors as sensor or analysis devices (Manz et al., 1990) such as μTAS or 2) post-integrating, for example, integrating MS to identify peptides.

The selection of the devices to measure depends on the specific implementation, for example, optical methods are favorable for biological application because they can be applied from a distance and do not need a direct contact. (Köhler and Henkel, 2005 and Guo et al., 2005) Six types of common used detections are classified (Vilkner et al., 2004); electrochemical detection, chemiluminescence and electrochemiluminescence, fluorescence, optical measurement, mass spectrometry, and other type such as temperature sensors; however, chemical types of sensors are recommended as a core for chemical analysis. (Bakker and Telting-Diaz, 2002)

In this section the review of miniaturized reactors as sensors and post-integration are presented. There are numbers of integrated devices reviewed but they only focus on application areas (Erickson and Li, 2004) and types of measurement devices (Bakker and Telting-Diaz, 2002; Vilkner et al., 2004; and Viskari and Landers, 2006) Therefore, in this report, the measurements of fundamental parameters in associated with miniaturized reactor are reviewed.

Pressure measurements

As this section started with a pressure measurement, it is a basic measurement for study fluid properties in the microreactor. Pressure sensors can be integrated into the MEMS devices while fabricating. (Jensen, 2006) For example, the pressure microsensors based on four piezoresistive sensing elements are bridged with the miniaturized reactor. (Lee et al., 2002) A pressure drop across the reactors makes an inverse stress in the piezoresistive elements and then affects to voltage and resistance change that can be measured. The pressure drop across the single microchannel can be related to fluid flow velocities because the combination of the absolute pressure and the pressure drop across the reactors can be determined the fluid flow velocities in microchannels. (de Mas, et

al., 2005) It is useful when the pressure drop is measured; the fluid flow velocities are also included.

Fluid flow measurements

Although, fluid flow is related to the pressure drop in the reactor but, alternatively, it can also be directly measured. In case of fluid that can be labelled with dye pigment, the integrated optical sensor can be used as optional measurement. However, for another fluid such as gases or unlabeled-dye liquids, florescence analysis is an alternatively popular approach because of its high-sensitivity, high resolution, and high selectivity. (Dettrich and Manz, 2006) The florescence can be detected by integrated optical sensor that uses total internal reflection to detect the structure of multiple phase flows in microchannels. (Kraus et al., 2004) Moreover, residence time distribution (RTD) can also be measured both in single-phase liquid and segmented gas-liquid flows by integrated florescence microscopy measurements. (Günther et al., 2004 and Trachel et al., 2005)

Temperature measurements

Temperature is other fundamental property that has been invented. Platinum temperature sensor is a propitious contact type of thermocouple materials because of its stability in the high temperature. Zou et al., (2005) presented miniaturized reactor integrated with Pt temperature sensor and heater that was controlled by PI and gain scheduling controller. This reactor can complete PCR with in 30 minutes and run parallel reactions independently at the same time. In addition, Tiggelaar et al. (2005a, b) invented the reactor that could be run in the high temperature by using Pt thin film buried in SiRn-tubes with corrugated zones. The reactor was reliable and run in the temperature more than 700ºC.

Alternatively, Fluorescence dye technique is also advantage for non-contact measurement because its signals can be detected and converted into 1D, 2D, and 3D images that is useful for studying temperature profile in the miniaturized reactor. For 1D and 2D temperature profile, Filevich and Etchenique (2006) used $[Ru(bpy)_3]^{2+}$ as the fluorescence dye and fiber-optic spectrofluorometer as the detector by using blue-LED as the exciting source. As for 3D image, Benninger et al. (2005 and 2006) used rhodamine B in methanolic solution as the excited dye and photocathode of a time-gated intensifier as the detector. All the signals from the detectors were converted into each 1D, 2D, and 3D images by the CCD camera.

Thermocouple and fluorescence techniques are the most favorable types of temperature sensors; however, there are many other types of integrated temperature sensors which are classified into contact and non-contact types and are reviewed by Yoo (2006). To date, only integrated temperature sensors are not enough, they also require an automatic temperature control or an integrated heating/cooling management technology for real-time implementation.

Chemical species detections

Fluorescence technique has been favorably applied for oxygen detection in cell cultivations. The oxygen detection in the form of dissolved oxygen (DO) has developed at NASA's lab to implement for cell culture in the space. (Gao et al., 2004 and 2005) The florescence quenching technique was used as the basic measurement by using tris(4, 7-diphenyl-1, 10-phenanthroline) ruthenium(II) chloride, $Ru(dpp)_3Cl_2$, as fluorescent dye that was coated inside the glass capillary tube. A blue-LED was used as an excitation light source and was detected by photodiode covered with long-pass optical fiber. The system showed long lifetime and stable while implementing in the space. Moreover, Kuang and Walt (2006) used the same type of indicator ($Ru(dpp)_3Cl_2$) to develop

fluorescence nanosensor and assigned to measure individual cell. Fluorescence signals from each cell were converted into images by camera recording. However, the same concept was applied by Sud et al. (2006) to monitor oxygen in term of images but they used ruthenium tris(2, 2'-dipyridyl) dichloride hexahydrate (RTDP) rather than $Ru(dpp)_3Cl_2$. Mehta et al. (2007) also used RTDP to quantitative measure and control oxygen level, and compared with the developed mathematical model. Both systems also represented long life-time implementation of fluorescence.

Glucose and lactate can be detected by integrated optical fibers. (Wu et al., 2005 and 2007) The detection is based on the color absorption, which the sample is mixed with the reagent in the microchannels, by connected the optical fiber to a green-light LED as a light source and changed the optical signal to a voltage signal. The system showed high accuracy, linear detection, short response time, and low limitation of concentration. As other method, Vojinović et al. (2006) developed the bienzymatic analyzed reactor based on immobilized horseradish peroxidase (HRP) as a sensor. Glucose-, alcohol-, lactate-, galactose-, and l-amino acid oxidases were deposited on HRP as sensors for glucose, ethanol, lactase, galactose, and amino acid, respectively. The reactor showed long lifetime, fast, cheap, and reliable for implementing.

Volatile aromatic compounds, benzene, toluene, and xylene (BTX) are the hazardous compounds that induce human carcinogen; therefore, the detection of these compounds should be investigated. Ueno's research group (Ueno et al., 2002) has investigated the detection of BTX by using porous silica powder in corporate with microfluidic devices; moreover, they can recently be portable the system into the automatic system. (Ueno et al., 2003) The devices composed of concentration and detection cells; the concentration cell was coated by silica adsorbent and the detection cell was associated by UV spectrometry. When a BTX mixed sample was injected, the sample was adsorbed on the adsorbent and then increasing the temperature to desorb the compounds. Because of its different thermal desorption, each compound was desorbed in different temperature and was sent to the detection cell. In addition, they also observed that the microporous silicate less than 1 nm affected the high benzene selectivity. (Ueno et al., 2004 and 2005)

The detection of chemical species is very important in biochemistry as well as in hazardous chemicals but, at the present time, there is still lack of verities of chemical species detection as well as the sensitivity of the detector that is the challenges in further inventions.

At the present, miniaturized fabrication technology has been inventing on the way to integrated sensors and analytical devices into miniaturized reactors. Although, the sensors/actuators can be installed into the reactor; however, there has still required methods to control these devices.

Control system for miniaturized reactors

Beside the integration of sensors and analytical devices, control of miniaturized reactor has also been required. Automatic control is one strategy that is an easy way for end users to implement the reactor. Soen et al. (2007) presented control strategies by using digital closed-loop design for micromachined accelerometer. Whereas field-programmable analogue array could be promised that the building plant way are changed like process design and control methodologies. (Palusinski et al., 2001) In summary, the advance in integrated circuit, embedded technology, new architecture, and control algorithm have been required for improving the control of miniaturized reactor. (Kothare, 2006)

V. FINAL REMARKS

Miniaturized reactor is still in the early stage of research and development. Because of a lot of its advantages such as small size, high surface-to-volume ratio, and safety, this is the one

technology that may impact the production market in many chemical, pharmaceutical, biomedical, and also microelectronic productions. However, the miniaturized reactor has still required many research areas to force it into the real production; the problems include production in high mass, comprehension in fluid flow dynamic, integration of analytic devices, and cure for clogging problem.

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