



Patenting trends in enzyme related microfluidic applications



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ABSTRACT

The miniaturization of continuous processes has been of interest in the academia and industry which is reflected by the increase in scientific publications and patent disclosures in the last decade. The aim of this study was to evaluate the patenting trends regarding enzyme related microfluidic applications in order to observe the progress of science and technology. The mapped patents have been classified as “immobilization method”, “biomolecule screening systems”, “integrated process development” and “microreactor design”. Half of the patent disclosures were filed by academia, whereas the other half was from industrial research which complies with the shift in microfluidics from academic and industrial research to commercial applications. Immobilization procedures carried out at room temperatures such as formulation of silica matrices using sol–gel technique, incorporation of novel hybrid materials, the integration of supercritical fluids and microfluidics, employing ionic liquids as wall-less microreactors, designing low cost, high performance microfluidic devices were the highlights which can pose challenges in various life science applications. The increasing trend is expected to continue and the presented state-of-the-art in enzyme related microfluidic applications have the potential to enhance industry’s capabilities for designing innovative systems which would demonstrate significant economic, societal and environmental benefits.

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1. Introduction

Following the Nobel Prize in Physics 1965 awarded jointly to Sin-Itiro Tomonaga, Julian Schwinger and Richard Feynman for their fundamental work in quantum electrodynamics, the capabilities of micro- and nanotechnologies for mechanical purposes have been exploited considerably leading to the progression of novel microfluidic applications. The first reported use of a microchip was in 1979 by fabrication of gas chromatograph air analyzer on a silicon wafer [1]. Miniaturized instrumentation has gained attention, particularly by performing flow through analysis on a chip [2] and rapidly grown with the introduction of integrated microfluidic devices which are typically referred to as lab-on-a-chip or micro total analysis systems (μ TAS). The design of highly efficient microfluidic devices have been applied in biochemical analysis, medical analysis, environmental monitoring, fermentation and life science applications such as detection kits, animal cell culture studies, enzymatic bioconversions, DNA analysis and polymerase chain

reactions. Micro reaction systems offer many advantages for chemical and biochemical reactions where large surface and interface areas are created providing rapid heat exchange and mass transfer that cannot be achieved by conventional batch systems. Additionally, flow pattern of solutions in a microfluidic system mainly form a laminar flow which allows strict control of reaction conditions and time.

Lately, a number of review articles, particularly focusing on enzyme immobilized microreactors using various techniques have been published [3–13] along with biochemical kinetics [14]. Although the previous studies dealt with the effects of miniaturization regarding the efficiency of the analytical method by applying well-known biocatalytic conversions, recent studies focused on screening the efficiency of the enzyme with an emphasis on kinetics and enzymatic synthesis.

The current review analyzes the contribution of patents to the advancement of enzyme related microfluidic applications starting from the first patent disclosures in 1998 up to the end of 2013. Retrieved data has been classified as “immobilization method”, “biomolecule screening systems”, “integrated process development” and “microreactor design”. The information revealed by patent disclosures together with recent publications was discussed

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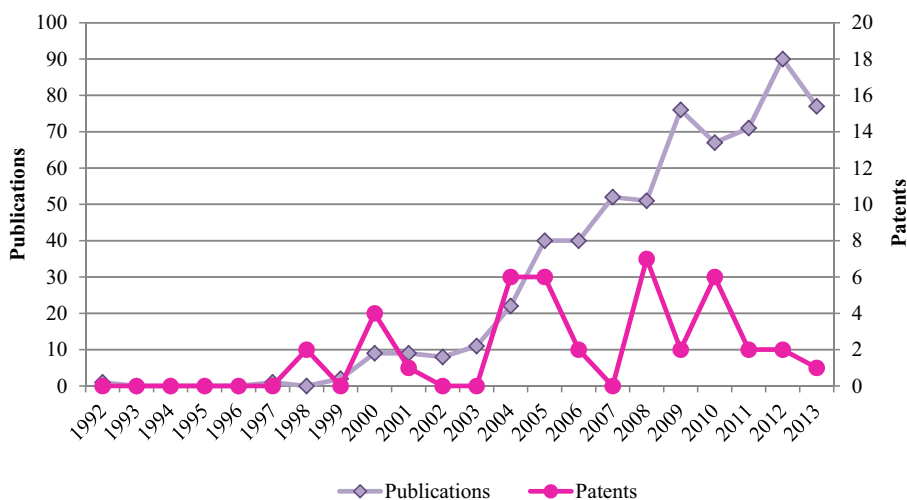


Fig. 1. Scientific and patent disclosures between 1992 and 2013.

to deduce trends in knowledge dissemination and commercialization.

2. Methodology

Scientific publications were statistically evaluated by using ISI Web of Science, whereas the source of the data for patent disclosures was the patent searching database, free patents online, where four keywords, namely 'enzyme', 'immobilization', 'microreactor' and 'microfluidic' retrieved from the abstracts. The US patents (USP), US patent applications, European (EP), Japanese (JP) patents and Patent Cooperation Treaty (PCT) applications were screened where a total of 94 patents were elicited applying various combinations of the keywords and the patents that had one or more priority numbers in common with a previously published patent were sorted out sizing down to 35 patents. Obtained data were processed using Bibexcel and Pajek softwares. Furthermore, elicited patents were categorized in terms of technical aspects reflecting the state-of-the-art.

3. Statistical insight to patenting trends

The increasing consumers' demands for new products to improve the quality of life have created many new challenges as well as opportunities for the industry. Biocatalysis has the potential to respond to variety of challenges providing new products to benefit from and therefore attracted considerable attention. However, the lack of a broad range of reaction platforms catalyzed by enzymes and the long development timelines are hindering the full potential of biocatalysis. Microfluidic systems can provide alternative routes for the development of enzyme processes which can be deployed to industry at shorter lead times.

This study has been carried out to analyze the knowledge created in enzyme related microfluidic applications where a significantly increasing trend was observed in terms of both scientific and patent disclosures from 2000 and on (Fig. 1) as a result of the intense nanotechnology initiatives in both fundamental sciences and engineering disciplines during the past decade. The results derived from mapping of the patents provided the preferences of various stakeholders in regards to empowering innovations in this particular field. The patents originating from United States (65.7%) were dominating, followed by those from Japan (17.1%) and the European Union (17.2%). Disclosures according to assignees were analyzed to identify the contribution of industrial and academic research to patented innovations. The results showed that

54.3% contribution arised from universities and research institutes, whereas 45.7% was from companies. The Bayh-Dole act permitted universities in the United States (US) to pursue the ownership of patents resulting from federally funded research and encouraged to be actively involved in patenting and licensing activities, which in turn increased the contribution of academia to product development [15].

The mapped patents were grouped in four categories in order to provide a holistic overview, where the patent disclosures related to providing methods for enzyme immobilization, integrated process development and microreactor design were about 28.5%, followed by biomolecule screening systems (14.5%).

4. A critical assessment of the elicited patents

4.1. Patent disclosures focusing on immobilization method

Enzymes can either be immobilized by entrapment in matrixes and surface modification of microreactor walls or dissolved in reactant solution and delivered to the microchannels when continuous operation mode is applied in microfluidic devices. If the latter is preferred, the enzymes have to be separated from the reaction solution by centrifugation or filtration. Although, the patent disclosures were simply related to physical or chemical incorporation of a reaction entity to a support material, the state-of-the-art was exceeded by utilizing photoactive compounds, emulsions and carrying out multistep enzymatic reactions. Following are the patents focusing on enzyme immobilization methods (Table 1).

By creating an analogy with capillary electrochromatography, a monolithic stationary phase was prepared in a capillary by photopolymerizing a mixture of monomers, porogenic solvents and photoinitiators at a wave length of 365 nm for about 5 min A freshly prepared solution of trypsin (10 mg/ml) in phosphate buffered saline (PBS) was flown through the polymerized sol-gel material while capping the ends of the capillary. Then enzyme filled capillary was left overnight at 4 °C after which the capillary was flushed with PBS and loaded into a column cartridge, ready for enzymatic reactions [16]. Japanese innovators from National Institute of Advanced Industrial and Technology [17] also focused on enzyme based silica nanoporous material composite by applying sol-gel method. The nanoporous material having pore diameters of 2–50 nm and a specific surface area of 200–1500 m² was loaded into a passage of the microreactor so as to exhibit interaction between the enzyme and the reactants. Another patent disclosure from the same National Institute in Japan [18] was related to immobilization of different

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