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Review

Process Intensification for Production and Recovery of Biological Products

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Abstract: Bioprocesses are important biological reactions which need several sophisticated methods and equipment to produce many novel and important compounds which some of them are traditionally produced by synthetic chemical reactions. In bioprocesses, the products are often produced in a dilute environment and finally they require a high purity. Because of that, downstream processes are usually included a large number of separation steps. Size and capital costs of the equipment are two main limitations of using bioprocesses at industrial scale. Bioprocess intensification by minimizing, substitution, moderation and simplification of the methods and equipment, drastically leads to sustainable processes. This study looks at intensification of the emerging equipment and operational methods and their advantages to lead smaller and cleaner bioprocess plants which in turn, increases production efficiency and quality and decreases byproducts formation, capital cost and energy consumption.

Keywords: Bioprocessing, Intensification, Energy, Equipment Size, Production Capacity

Introduction

The need for sustainable, efficient and cost effective processes are in demand for many chemical and biological industries (Wohlgemuth, 2009). Several alternatives have been developed to address some of the problems associated with the use of the conventional apparatuses and techniques. Process Intensification (PI) has been known as a method to comply with such requirements (Lutze *et al*., 2010). Process intensification as a method for making significant changes in the size of a process plants to achieve a given production objective. These reductions can come from decreasing the size of individual equipment or from removing the number of involved unit operations (Stankiewicz and Moulijn, 2000). PI may be defined in a number of ways. One of several definitions of PI sets out a selection of all themes is that "Any chemical engineering development that leads to a substantially smaller, cleaner, safer and more energy efficient technology is process intensification" (Reay *et al*., 2013). PI refers to replace complex technologies with integrated equipment and processes that are smaller in size, less costly and more efficient (Charpentier, 2007). Preferably, it integrates as many unit operations as possible into a multifunctional ones to be used in the chemical and biological industries (Marques and Fernandes, 2011). Environmentally, however, the most telling impact of PI is likely to be in the development of reactor designs for truly green technology. It is well understood that the reactor is the heart of any chemical process, as it dictates both the product quality and the extent of the downstream separation and treatment equipment. Designing reactors which operate intensively and which give high conversion and selectivity with minimal by-product formation will permit us to approach the green ideal of delivering a high quality product without an extensive downstream purification sequence. Among the

processes, biological processes need more sustainable production methods and technologies (Clark *et al*., 2009; Wohlgemuth, 2009). In this article, we take a closer look at bioprocess intensification. We define what it involves and review recent developments in bioprocess-intensifying devices and methods.

Bioprocess Intensification

A growing tendency towards the use of sustainable resources and production technologies has attracted attention (Van Hecke *et al*., 2014). Intensive bioprocessing, therefore, has been the subject of many contributions at PI conferences since 1995 (Reay *et al*., 2013). Bioprocess Intensification (BI) aims to accelerate the overall processing time and/or reduce reactor volume (Akay *et al*., 2005). A wide range of intensification methods can be used in bioprocessing. Membrane reactors, jet loop and biocatalyst membranes are available for intensify biochemical processes (Akay, 2005). Supported biocatalysts strategies are often used to further improve the catalytic activity and strength of enzymes and microorganisms (Akay *et al*., 2005). The whole field can be divided into two main areas: (i) Equipment intensification, such as use of novel reactors, heat exchangers and mass transfer units; and (ii) process intensification, such as use of new separation strategies, integration of reaction and separation, phase transition, techniques using alternative energy sources and new control methods. Distinctive features of the process-intensifying methods are summarized in the following subsections.

Equipment

PI significantly enhances transport rates and it gives every molecule the same processing experience. This definition can be usefully interpreted as being a process development involving dramatically smaller equipment which leads to: Improved control of reactor kinetics giving higher selectivity, reduced waste products, higher energy efficiency, reduced capital costs and reduced inventory, improved intrinsic safety and fast response times. Low and uniform shear is one of the important parameters that should be considered in bioprocesses especially when handling shear-sensitive materials, such as certain pharmaceutical crystals and in flocculators (Ni *et al*., 2001). Intensifying equipment in bioprocesses used to enhance heat transfer and gas-liquid mass transfer which is often the limiting factor in aerobic systems (Reay *et al*., 2013).

Mixers are fine examples of process-intensifying equipment. The technology of stirring liquid-liquid and gas-liquid systems has been greatly intensified during the past years. Microreactors which usually have a sandwich-like structure consisting of a number of layers with micromachined channels (10-100 μm in dia) can be used for multiple functions such as mixing, heat exchange and catalytic reaction. Integration of these various functions within a single unit is one of the most important advantages of microreactors. These reactors due to their unique specifications allow for operating highly exothermic processes isothermally (Stankiewicz and Moulijn, 2000). Intensification equipment used in bioprocessing is shown in Table 1.

Table 1. Intensification equipment used in bioprocessing

Equipment for carrying out chemical reactions	Equipment for operations not involving chemical reactions
Spinning disk reactor	Static mixers
Static mixer reactor	Compact heat exchangers
Static mixing catalysts	Microchannel heat exchangers
Monolithic reactors	Rotor/stator mixers
Microreactors	Rotating packed beds
Heat exchange reactors	Centrifugal adsorber
Supersonic gas/liquid reactor	
Jet-impingement reactor	
Rotating packed-bed reactor	

Table 2. Intensification methods used in bioprocessing

Multifunctional reactors	Hybrid separations	Alternative energy sources	Other methods
Reverse-flow reactors	Membrane absorption	Centrifugal Fields	Supercritical fluids
Reactive distillation	Membrane distillation	Ultrasound	Dynamic (Periodic)
Reactive extraction	Adsorptive distillation	Solar energy	Reactor operation
Reactive crystallization		Microwaves	
Chromatographic reactors		Electric fields	
Periodic separating reactors		Plasma technology	
Membrane reactors			
Reactive extrusion			
Reactive comminution			
Fuel cells			

Methods

A wide range of intensification techniques can be used in bioprocessing ranging from high gravity fields, electric fields and ultrasound, to membrane processes and some reactors. Most process-intensifying methods as shown in Table 2 are categorized into multifunctional reactors, hybrid separations and alternative energies for processing.

Application of PI in Biological Processes

Today, a huge research effort is devoted to BI methods. BI methods cause many advantages. Membrane bioreactors, for instance, can be used for selective *in-situ* separation of the reaction products and to enhance selectivity or yield of a process or to improve mass transfer (Stankiewicz and Moulijn, 2000). Using immobilized cells bioreactors have advantages as compared to free cells bioreactors. Immobilized cell systems allows the use of independent growth rate bioreactors. In addition, catalytic stability are usually greater for immobilized cells than free cells. Some immobilized microorganisms tolerate higher toxicity levels as compared to free cells (Akay *et al*., 2005). Table 3 shows an overview of the various intensification processes that are or can be used in bioprocesses and their intensifying effect on the processes.

The Advantages of PI

While size and capital cost reduction were the original target for PI, it quickly became apparent that there were other benefits, some of which have become even more important since PI was conceived. BI results to a significantly smaller size, greener, safer and more efficient technology. Furthermore, PI significantly reduces the time to market, which is the key issue in some sectors such as fine chemicals and biological industries.

Since the essential idea of PI is a large increase in production per unit plant volume, it also results in significant reduction in residence times (typically from hours to seconds for some operations). This has profound implications for the plant's ability to respond quickly to desired process changes in general and for the control philosophy in particular. In any event, it will become possible to switch product grades rapidly with little intermediate off-specification product being generated. Some of distinctive benefits are summarized in the following subsections.

Safety

Approaches to the design of inherently safer plant could be grouped into four major strategies: Minimizing, substitution, moderation and simplification. Given the anticipated reductions in plant volume through PI methods, the toxic and flammable inventories are correspondingly reduced, thereby making a major contribution to intrinsic plant safety. PI can also allow one to moderate conditions to minimize risk of explosions and to simplify processes by having fewer unit operations and less complex plant (Hendershot, 2003).

The Environment

There are recommendations by the UK Royal Commission on Environmental Pollution that we need to reduce CO_2 emissions by more than 50% in order to stabilize their impact on global warming (DECC, 2012). CO_2 gas is believed to be the principal gas contributing to this phenomenon. So, one of the most interesting and challenging areas of technology is Carbon Capture (CC), normally combined with storage in most literature (Wang *et al*., 2011). Most current CC plants use old chemical engineering technologies such as static absorption/desorption towers for the most common form of carbon capture, post-combustion capture using absorption of the CO_2. CC could become one of the most important applications of PI within the next two decades. The application of PI here is directed at reducing the sizes of the absorption and desorption columns, for example, by carrying out the processes in rotating packed beds and by using compact heat exchangers in other parts of the plant. Other methods involve membranes and intensified adsorption reactions. The rotating packed bed has been examined in Europe and in China in this respect (Cheng and Tan, 2009; Yi *et al*., 2009). Interestingly, a survey on attitudes to PI revealed that a change to a non-carbon based economy would be a major stimulus for PI (Nikoleris *et al*., 2002; Reay *et al*., 2013). These observations lead us neatly into the discussion of the ways in which PI can benefit energy use, which, of course, impacts on the environment in a number of ways, in particular, in carbon emission mitigation.

Energy

The effectiveness of any PI strategy is ultimately dependent upon success in identifying techniques for dramatically increasing the intensity of the fluid dynamic environment, so as to accelerate the transfer of heat, mass and momentum within a process or operation. The energy savings are largely due to better selectivity and reduced energy use in separation processes, as well as improved control. The UK carried out an assessment of the potential for PI energy savings some years ago. The UK Energy Efficiency Office supported the development of strategies in three areas (i) compact heat exchangers; (ii) heat and mass transfer enhancement; and (iii) process intensification related to saving energy. Compact heat exchangers and in some cases combination of heat exchangers with other alternative energy sources such as microwaves show energy efficiency benefits. Micro-

fluidic processes (reactions which occur at a micro scale) help to improve energy efficiency, mixing and product yield. There are many practical challenges to overcome in applying these processes to industrial applications, particularly in scaling-up from small volume to bulk manufacture. As part of these strategies, studies were carried out by Linnhoff March, of the energy savings made and data are given in Table 4.

Table 3. Overview of the various applications of intensifying processes which can be used in bioprocesses

Equipment	Typical applications	Results of the study	References
Higee Bioreactor (HBR)	Polyhydroxyalkanoate (PHA) production through fermentation	Higher mass transfer capability, improved biomass concentration and PHA yield	(Boodhoo *et al*., 2010) (Feng *et al*., 2013)
Spinning Cloth Disc Reactor (SCDR)	Enzymes immobilization	Higher mass transfer rates and rapid mixing	
Static mixer	Multiphase reactions	Higher mass transfer	(Al Taweel *et al*., 2013)
Micro-reactors	Drug and fine chemical manufacture	Improved diffusion	(Reay *et al*., 2013)
Monolithic reactors	1. Enzymatic oxidation of glucose 2. Gluconic acid formation by gloconobacter suboxydanse 3. Hydrogen production by *Clostridium butyricum*		(Dunford, 2012)
Heat exchange reactors	Fast exothermic reactions nitration, azo coupling, halogenation, hydrogenation oxidation, sulfonation amination and alkylation	Safer processing, Better economics and More energy-efficient	(Anxionnaz *et al*., 2008)
Microchannel reactor	Synthesis of metallo-organics, Radical acrylate polymerization, Liquid-phase reactions (catalytic or non-catalytic), Gas–liquid reactions (halogenations, nitrations) and Gas-phase reactions (oxidations, hydrogenations)	Easily and efficiently heat transfer, Improved control of transfer processes and heat management, Increase the process selectivity and product purity	(Anxionnaz *et al*., 2008)
Electrically enhanced reactions	Bioreactions, break up droplets into micron sizes, Hydrolytic splitting of esters to yield free fatty acids and glycerol	Enhancement of heat and mass transfer	(Reay *et al*., 2013)
Continuous stirred tank reactor	Crystallisation, bioreactions, hazardous reactions, general pharmaceutical and fine chemical reactions	Overcomes batch limitations, cheap, can be used in series, easy to clean, better temperature control than batch STR	(Reay *et al*., 2013)
Structured packing	reactions involving slurry catalysts	Better mixing and radial heat-transfer	(Stringaro *et al*., 1998)
Oscillatory flow screening meso-reactor	Production of an aroma compound γ-decalactone using *Y. lipolytica* cells	50% reduction in time to required conversion, enhance liquid–liquid mixing	(Reis *et al*., 2006)
Fixed-bed bioreactor using micro-cellular polymer-immobilized cells	production of α-amylase by immobilized *Bacillus subtilis* in porous polymeric polyHIPE	Retain the producer cells without any clogging the matrix	(Jimat, 2011)
Flow-through monolithic microbioreactors with immobilized cells	phenol-degrading bacteria, *Pseudomonas syringae*,was immobilized in microbioreactor in monolithic form	The control of bioreaction can be carried out at a microscopic level, the reactor volume is drastically reduced, therefore providing all the advantages of classical process intensification technology	(Erhan *et al*., 2004)
Enzymatic membrane reactor	Enzymatic hydrolysis of casein	Residence time required is reduced and the utilisation of substrate substantially increased	(Trusek-Holownia, 2008)
Micro-cellular polyme	Microcellular polyHIPE polymer supports osteoblast growth and bone formation in vitro	Significant increase in osteoblast numbers penetrating into the polymer, highly porous scaffold with a potential for bone tissue engineering	(Akay *et al*., 2004)
Methods			
enzymes immobilization	Immobilization of glucose isomerase (on an inorganic carrier) for production of high fructose corn syrup, penicillin G acylase(covalently attached to polyacrylate) for the production of semi-synthetic penicillins, lactase(on an ion-exchange resin) for producing low-lactose milk, TL lipase (on silica) for fat modification	Obtaining adequate productivity, improvements in activity, stability and selectivity	(Drauz, 2012)
Cells immobilization	Beer fermentation using immobilised yeast cells	High-productivity	(Verbelen *et al*., 2010)
Rotating bed of porous packings	Using a rotating bed of porous packings for application to an *E. coli* batch fermentation process	Intensification of gas–liquid mass transfer Higher overall *E. coli* cell growth rate	(Boodhoo *et al*., 2008)
Membrane based processes	Lactic acid production	Continuous removal of lactic acid from fermentation broth Fermentation is carried out in a continuous mode Higher productivity	(Pal *et al*., 2009)
Reactive crystallization	Efficient calcium lactate production by Fermentation coupled with crystallization-based *in-situ* product removal	Higher average productivity	(Xu and Xu, 2014)
Membrane absorption	Recovery and purification of biofuel compounds, including ethanol, iso-propanol, n-propanol, iso-butanol, n-butanol, 2 methyl-1-butanol, 3-methyl-1-butanol and n-pentanol	Economic recovery	(Nielsen *et al*., 2010)
Liquid-liquid extraction	*In-situ* product removal of phenol from *P. Putida* S12TPL fermentations Recovery of fermentative carboxylic acids	Increased yields and productivity	(Heerema *et al*., 2011; López-Garzón and Straathof, 2014)
Ultrasound	Shikonin production in *L. Erythrorhizon* cell cultures	Enhance shikonin production in cell cultures, increased extraction yield from 20 to 65-70%, due partially to an increase in the cell membrane permeability by sonication	(Cai *et al*., 2012)

Table 3. Continue

Membrane absorption	*In-situ* Product Recovery of n-Butanol *In-situ* product removal of phenol from *P. Putida* S12TPL fermentations	Enhancing the yield of n-butanol and economical purification Increased yields and productivity	(Nielsen and Prather, 2009; Heerema *et al*., 2011)
Electrodialysis	Recovery of pyruvic acid from fermentation broth Recovery of fermentative carboxylic acids	Separate pyruvate without using solvents, to concentrate the product and to minimize process waste-water	(Zelić and Vasić-Rački, 2003)
Membrane extraction	Removal of inhibiting products from a fermentation broth	Reduce the fouling and improve the filtrate flux	(Heerema, 2012)
Anion exchanger-based	Microbial production of propionic acid with *Propionibacterium freudenreichii*	Increased productivity and product yield, with a corresponding decrease in the number of downstream processing steps, as well as in substrate consumption	(Wang *et al*., 2012)
Adsorption	Fumaric acid recovery from fermentation broth Recovery of fermentative carboxylic acids	Increased the yield and productivity	(Xu *et al*., 2012; López-Garzón and Straathof, 2014)
Adsorption-desorption	*In-situ* recovery of 3-hydroxypropionaldehyde (3HPA) during biotransformation of glycerol by *Lactobacillus reuteri*	2 times higher productivity of 3HPA	(Sardari *et al*., 2014)
Dynamic fermentation	Simultaneous biosynthesis and recovery of menaquinone-7	Enhanced yield of fermentation process, with a corresponding decrease in the number of downstream processing steps	(Berenjian *et al*., 2014)

Table 4. Potential energy savings due to investment in PI in a range of process unit operations

Process	Energy saving (PJ/a)
Compact heat exchangers	16.0
Separators	6.2
Reactors	11.0
Overall plant intensification	40.0 (technical potential)
Effluent treatment	1.0

Future of BPI

Several authors have emphasized that PI has, or will have, a major role to play in the future of chemical and biochemical engineering. The phrase ‘molecules into money’ was used in proposing that chemical process engineering drives today’s economic development and wealth creation, the process engineering being, of course, based on PI. Despite the compelling benefits of PI for the process industry it has to be admitted that there have been and still are, serious obstacles which have been responsible for its relatively slow adoption since its inception around two decades ago. In the context of an existing fully established and depreciated plant, it is extremely difficult to introduce unproven intensified equipment. The conservatism of plant owners using batch processes means will not easily accept continuous processing solutions. A mature technology in the process industry is usually associated with the existence of design codes and packages. A developing technology such as PI is not yet embodied in such design codes. The provision of this information is an important next step for the relevant equipment vendors. PI modules should be incorporated into relevant university courses and students must be encouraged to question conventional thinking and be given the chance to experiment with intensified equipment. Another important factor involves the lack of demonstration facilities in which clients’ processes may be performed on intensified equipment. A successful outcome to such trials is a very powerful motivator for the adoption of the new technology.

Conclusion

Challenges in the industry such as competitive products for the same indication or desired cost reductions are forcing many researchers to explore new production options. Process intensifying equipment such as novel reactors and process intensifying methods such as new separations are expected to bring significant improvements in energy saving, safety, company profitability, equipment size, production capacity and waste production of the processes. However, there are also limitations to PI and an awareness of these is essential if correct application is to be ensured for the future of sustainable process engineering.

Author’s Contributions

All authors contributed extensively to the work presented in this paper.

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