CHAPTER 11

Process Intensification of Immobilised Enzyme Reactors

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Chapter abstract

The advantages of enzyme catalysis are high specificity and (enantio) selectivity resulting in reactions with little or no by-products. The applications of enzymes in aqueous medium are well established and have been extended to organic synthesis more recently. The two limiting factors for large scale application of enzymes are continuous processing and process scale-up. Process intensification has the potential to overcome these challenges posed by conventional processing methods by incorporating a novel reactor design or by using alternate processing methods. Process intensified reactors like membrane reactors, microreactors, monolithic reactors and rotating disc reactors for enzyme catalyzed reactions will be discussed in this chapter. These reactors have shown an improved performance compared to the enzymatic reactors currently in use and future opportunities include application for enzymatic catalysis on an industrial scale and advances in reactor design and process control.

11. Process Intensification of Immobilised Enzyme Reactors

11.1 Introduction

Enzymes belong to the protein family and can catalyze chemical and biochemical transformations that take place at room temperature and pressure[1]. Enzyme catalyzed reactions have found a number of applications in the food and pharmaceutical sectors due to their biocompatibility with the human body. More recent application of enzyme catalysis includes synthesis of intermediate scale chemicals[2-4] and production of polymers[5-7]. However, the reactions have only been carried out on a bench scale and industrial application has been limited by a decrease in reaction yield and selectivity during scale-up[8,9].

One way towards a more sustainable future is to change the current unsustainable practices in process industries. Process intensification (PI) can reduce process inefficiency[10] by transforming the current engineering practices to make it more sustainable and environmentally benign without hampering production efficiency and profitability[8]. PI can be achieved in the form of novel/hybrid reactor design or by novel processing routes. The underlying features of these reactors include intensification of mass and heat transfer accompanied by minimum downstream processing. The aim of this chapter is to introduce a range of new reactors that have been developed since the early 90's. These reactors have been used to improve existing reaction mechanisms and also to enable scale-up of more novel applications like enzyme catalyzed reactions. Other chapters in this book (see chapters 9 and 12) deal with alternate energy source for enzyme reactors like microwave and ultrasonic energy to achieve PI.

This chapter will firstly provide an overview of enzyme immobilization and conventional reactors with their shortcomings. Thereafter, process intensification of reactors with a focus on immobilized enzymes will be discussed although some of the reactors support both free

and immobilized enzyme reactions. This chapter will conclude with a perspective on the future opportunities for process intensified enzyme reactors.

11.2 Enzymes as catalysts

Enzymes are natural catalysts that have gained importance for improving chemical reaction rates and have the potential to surpass the catalytic activity of inorganic catalysts. They are highly specific catalysts operating under mild reaction conditions and their chirality enables them to be employed for enantioselective synthesis in pharmaceutical industry, where end products of high optical purity are desirable. Reactions catalyzed by free enzymes follow a simple operation protocol; however, the key drawbacks with free enzymes are the deactivation under harsh operating conditions and the additional separation step at the end of the reaction. Immobilization of enzymes broadens enzyme applicability and mitigates the issue of instability[11] due to the increased mechanical and thermal stability provided by the support material, which also facilitates enzyme recovery and reuse. Enzyme immobilization methods can be broadly classified as below (Figure 11.1).

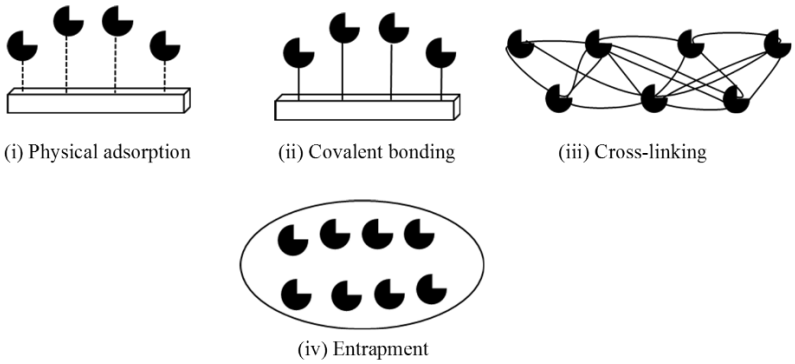

Figure 11.1 Classification of enzyme immobilization methods

An in depth analysis of immobilization techniques is beyond the scope of this chapter, and has been published by the author[12]. Briefly, enzyme immobilization can either be physical or covalent in nature. Physical binding of enzymes involve ionic, van der Waal's or

hydrophobic interactions with the support surface. The method is simple and cost-effective, but enzyme leaching and instability in the reaction environment is a key drawback[13]. Covalent binding of enzymes provides better enzyme stability and greater re-usability in both aqueous and organic media. Chemical modification of the enzyme during the process of immobilization is one of the main disadvantages[14]. Enzyme entrapment within a polymeric network or sol-gel is another immobilization technique, where the enzyme is safeguarded against mechanical shear and hydrophobic solvents. Increased resistance to mass transfer and low enzyme loading are some of the drawbacks of this method[15]. Carrier free immobilization is possible by using a cross-linking agent like gluteraldehyde, which binds the enzymes to each other without the need for a support. Reports of higher enzyme stability and activity have been reported for cross-linked enzymes. However, some of the cross-linking agents are specific for certain enzymes and it is necessary to optimize the amount of crosslinking agent as an excess can adversely affect the enzyme activity and productivity[16].

11.3 Enzymatic reactors: Conventional vs Process Intensified Reactors

This section will focus on the most commonly used enzyme reactors including batch, packed bed and fluidized bed reactors and some of the short comings, which have led to the need for process intensification in bioprocessing.

11.3.1 Conventional reactors and Enzyme Catalysis

Batch stirred reactors (BSTR) used to be the popular choice for enzymatic reactions. These are useful to test novel reactions with low reaction volumes and they have been employed for both free and immobilized enzyme catalysis[17, 18]. However, there are inherent problems like enzyme separation and recovery from the reaction medium, low productivity due to the time consuming operations of filling, emptying and cleaning the reactor between batches[19].

Another commonly used reactor for large scale enzyme catalysis is the packed bed reactor (PBR), in which the enzyme is immobilized on a support, which is packed in a column or a pipe. The PBR provides a large interfacial area, easy catalyst recovery and re-usability due to using immobilized enzyme and the structured enzyme packing allows for excellent contact between the enzymes and the substrate in comparison to stirred tank reactors. An additional advantage is the elimination of by-products to a large extent[20]. Successful applications of PBR include production of biodiesel[21], lipid hydrolysis[22] and acidolysis of oil[23]. The key disadvantage is the increase in pressure drop, especially for small sized packings. Also, the availability of enzyme per unit volume in the reactor is reduced with an increasing packing size, thereby, reducing the efficiency of the reactor volume[24].

The fluidized bed reactor (FBR) is a form of packed bed reactor, but the catalyst is in a fluidized state due to the counter-current contact between the packing and the fluid phase[24]. Continuous agitation of the solid and the liquid phase ensures a uniform temperature distribution, but may lead to catalyst leaching and agglomeration. These reactors have been used less in comparison to PBRs for enzyme catalyzed reactions. A higher conversion and a lower pressure drop for the enzymatic hydrolysis of oil was found in the FBR in comparison to the PBR[25], and the interesterification of oils, was carried out successfully in the FBR but not in the PBR due to a higher pressure drop[26]. The main disadvantage of the FBR is the need for large packing size reducing the enzyme loading per unit volume and the overall efficiency of the reactor as well as an increased risk of bypassing and channelling of both liquid and gas phases[27].

To summarize, though conventional reactors have been successfully used for enzymatic reactions to produce the desired product, problems associated with scale-up, product purification and mass transfer limitation in particular, have been the driving force for identifying alternate reactor design to effect process intensification.

11.3.2 Process Intensified Enzymatic Reactors (PI-ER)

Process Intensification (PI) can achieve the control of chemical reaction on a molecular scale and the advantages are: (i) enhanced reaction rate with a reduction in the size of process equipment, (ii) increased selectivity of the product resulting in waste reduction, (iii) easy product separation, which otherwise is responsible for major energy consumption, (iv) manufacturing process for novel and advanced products can be better tailored[28]. PI can be achieved either by modification of the reactor design or by changing the operating parameters used. Modification of existing reactor design has led to a new class of hybrid reactors incorporating membranes, monoliths, microchannels and rotating discs and these will be focused in this chapter. These reactors have the potential for enhancing the overall reaction rate by increasing the effective transport rates and/or by providing multi-functionality to devices for process, which can benefit from improved reaction engineering[29]. The aim of this chapter is to highlight the recent developments in the field of PI-ER. Among the different PI-ERs, enzymatic membrane reactors (11.3.2.1) and microreactors (11.3.2.2) are well researched while monolithic (11.3.2.3), rotating packed bed (11.3.2.4) and spinning mesh disc reactors (11.3.2.5) are novel classes of reactors for bioprocessing.

11.3.2.1 Enzymatic Membrane Reactor (EMR)

Enzyme Membrane Reactors (EMR) have gained popularity for catalyzing bioconversions since the first enzyme immobilization took place in the 1950s. There are two ways in which the enzymes can be incorporated in the EMR: (i) suspension in the solution which is in turn compartmentalized by the membrane (Figure 11.2a) and (ii) immobilization within the membrane matrix (Figure 11.2b). The first configuration is analogous to an integrated stirred tank reactor - membrane separation unit, while in the second configuration, the membrane functions both as a catalyst support and as a separation medium[30].

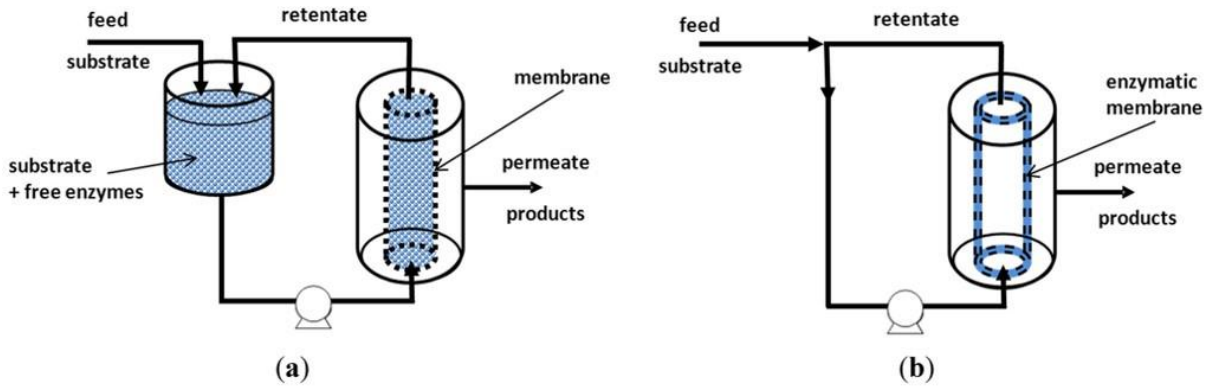

Figure 11.2: (a) Free enzyme membrane module and (b) Membrane immobilised with enzyme module. Adapted from[31]

The driving force in these reactors can be pressure, electric or chemical potential. EMR has the potential to circumvent the disadvantages of conventional enzyme reactors due to the following attributes:

- EMRs allow for continuous mode of operation and is supported for both free and immobilized enzyme reactions[32].
- The combination of chemical reactions accompanied by in-situ product separation result in an increased reaction conversion. This also simplifies enzyme recovery and reuse[33].
- The selectivity of the reaction can be improved and tailored by optimizing the enzyme-membrane combination[34].
- The moderate operating conditions ensure enzyme activity is not lost due to high temperature and pressure[32].
- EMRs are attractive for enzymatic reactions on an industrial scale as they are a greener alternative to the existing technologies in terms of energy saving and process waste reduction ensuring production of end products with high purity[35].

The selection of the membrane depends on the nature and size of substrate, enzyme and product(s). Ultrafiltration membranes are mostly used for reactors employing free enzymes as their pore size range (1 to 100 nm) is sufficient to retain a wide range of enzymes and the unique asymmetric pore size distribution along the length of their surface allows for higher flow rate of the permeate, reducing clogging and hence, allowing for easy cleaning of the membrane[36, 37]. The enzyme stability on a particular membrane is critical, and the choice of membrane material is usually made based on membrane characteristics, like pore size distribution, molecular weight cut off, operating pH, temperature and pressure and resistance to chemicals[36, 38]. Ceramic membranes are generally preferred to polymeric membranes as they provide greater chemical resistance and can operate at higher temperatures and pressures although the uptake of polymeric membranes is increasing and there is a lot of research focusing on improving the operating envelope of polymeric membranes[37, 39].

EMRs are conventionally classified based on the reactor configuration and the hydrodynamics of the system, into CSTR and plug flow EMR. However, with the advent of multi-phase reactor configurations and different membrane configurations, more recently they have been classified as direct contact, diffusion and multiphase EMRs[40].

i. Direct contact membrane reactors

In this reactor configuration, the substrates are introduced on the enzyme side of the reactor, where the enzyme is either free or immobilized. Further classification of this configuration include dead end, recycle and dialysis reactors. In the dead end cell reactor configuration, both separation and reaction take place in a single compartment and pressure is used as the driving force to cause the permeation of the reactant media across the membrane. The mode of operation of this configuration is analogous to a stirred tank reactor, where the membrane divides the permeate and the retentate stream. Despite shortcomings such as low flux and

membrane surface area, this configuration is popular for lab scale processes as a consequence of operation simplicity[41, 42]. In the recycle reactor configuration, the solution containing substrate and the enzyme are recycled between the reaction vessel and the ultrafiltration membrane unit, present in a closed loop. In dialysis reactors, enzyme and substrate is introduced on the same side of the membrane and the product(s) diffuse across the membrane because of the concentration gradient. Tubular and hollow fibre membranes are the commonly used membrane modules for the reactor configuration in general for applications like hydrolysis of lipids and proteins and enantioselective synthesis of protein[43-46].

ii. Diffusion membrane reactors

In this class of reactor configuration, the enzyme and substrate are separated by the membrane, and the substrate diffuses through the membrane enabling the reaction. The products are then recycled back to the substrate side after reaction. Hollow-fibre modules with the enzyme placed in the shell side is usually used for this configuration[40]. Only substrates with low molecular weight can be processed, and since diffusion of the substrates into the permeate side is the rate limiting step, reaction rates are lower in this configuration[30]. This configuration has mainly been used for enzymatic conversion of sugars[47] and synthesis of proteins[48]. The limited applicability of this configuration is one of the main drawbacks.

iii. Multiphase enzyme reactors

The final configuration is characterized by the interfacial contact between the enzyme and the substrate at the membrane site. The membrane separates the polar and the apolar phases and in some cases, slight pressure is applied to facilitate the phase separation. The flow can either be single pass or recycled through external vessels. This configuration is used when the enzyme is triggered by interfacial activation[43]. The applications of this reactor configuration

include oil hydrolysis[49-51] and synthesis of fatty acids[52-55]. Phase mixing is one of the key disadvantages of this configuration.

EMRs have been applied for the production of pharmaceuticals[56-58] achieving high enantiomeric excess ('ee'). In the food sector[59, 60], EMRs have been used for clarifying fruit juices and lactose reduction in dairy products. Enzymatic hydrolysis of lipids is another successful application of EMRs[50, 61,62]. In general, immobilized enzymes have a higher stability compared to when the reactor was operated with free enzymes. An increase in yield has been achieved by increasing the enzyme loading on the membrane. Furthermore, in EMRs that incorporate nanofiber membranes, the transmembrane pressure effect on conversion and energy consumption was eliminated.

Though membrane reactors have been used in many successful transformations, EMRs still have a range of shortcomings[32] such as a loss in the enzymatic activity due to immobilization or the reaction environment, and membrane fouling. Future research should focus on making advances in reactor design and control mechanism for reactor scale-up and improving the reactor efficiency by carrying out cascade and synergistic reactions and reducing fouling, for example by using tuneable membranes. EMR technology can also be extended to reactions with insoluble products to explore the potential of the UF membrane to retain solid particles[40].

11.3.2.2 Enzymatic Microreactors

Microreactors are a type of reactors that comprise of microchannels of diameter between 10-500 µm, which reduce transfer limitations and enable a greater exchange area for reactant molecules (Figure 11.3). This in turn improves mixing and heat exchange within the microchannels resulting in higher mass and heat transfer[63], resulting in fast reactions with

residence times in the order of milliseconds using small amounts of enzyme and substrate for the reaction.

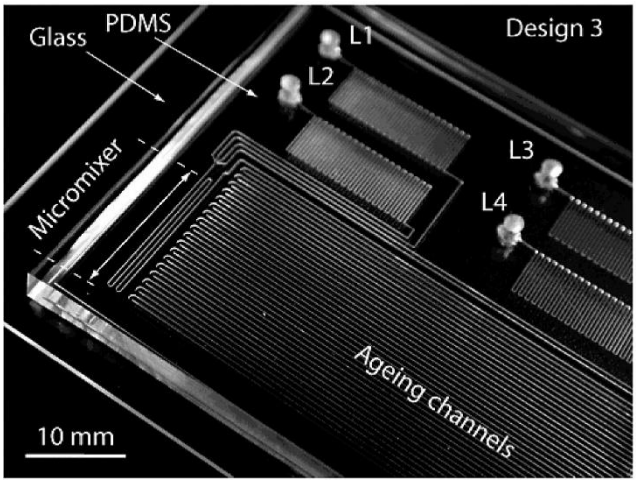

Figure 11.3 A PDMS and glass microreactor. Reprinted (adapted) with permission from Mason et.al © 2007 American Chemical Society.

Microreactors have been well developed for analytic and diagnostic applications[37, 64-66] and the opportunities for bioprocessing are gaining attention due to the following PI advantages:

- Enhanced reaction selectivity can be obtained using microreactors as energy can be supplied in the right form and in the right amount; thus, achieving a uniform reaction experience for all the reactant molecules[28].
- In addition to providing superior heat transfer, free radicals are terminated when they come in contact with the microchannel walls, stabilising their propagation rate[67].
- Miniaturization of the reactor reduces the energy consumption, waste generation and chemical inventory as the reaction volumes are reduced ensuring that the reactor volume is fully utilized[68].

- Scale up can easily be achieved through the replication and numbering up of each reactor unit, and thus, reducing the cost associated with re-design which facilitates faster commercial scale production[67].
- Allows for fast screening of small molecules for drug discovery for the pharmaceutical industries, which is otherwise limited by conventional batch reactors and their associated higher chemical inventory and safety concerns[39].

Though free enzyme catalysis is possible in the microreactor, one key component is the immobilization of enzymes, with a wide range of techniques having been reported. Physical immobilization of the enzymes on the surface of SiO_2[69], PDMS[70] and fused silica[71-73] has been successful. In all the cases, the enzymes were protected from getting denatured and could be used for multiple cycles without a significant loss in the enzymatic activity. A higher enzyme loading has also been achieved with fused silica as a higher surface area was available within the sol-gel modified surface although these techniques require several steps and are limited to a narrow range of enzymes. Enzyme entrapment[74] and encapsulation[75] (within a polymer matrix or silica) followed by immobilization on the surface of micro-reactor channels is another well reported technique. These microreactors were compatible with organic solvents and were used over multiple reaction cycles[49], although the preparation involved several time consuming steps and the enzymes were often denatured during the immobilization. Adsorption[76] and cross-linking[77] of enzymes incorporated within the walls of a microreactor has shown to provide solvent compatibility and longer enzyme activity. However, enzyme leaching and reduction in the enzyme functional groups is a common problem with this method.

The applications of enzymatic microreactors can be classified based on (i) catalytic biotransformation of substrates and (ii) kinetic screening of substrate molecules. An example of free enzyme reaction is electrophoretically mediated microanalysis, which is carried out by

making use of different zones of mixing within the microchannel based on the mobility of the enzyme and the substrate molecule[78, 79]. Exciting opportunities include the tandem synthesis of pharmaceuticals using two microreactors in series. This exhibited higher conversions at lower reaction times in comparison to batch reactors in series[80]. Another interesting application is for complex reactions like chemo-enzymatic synthesis, which has converted simple substrates to polymers[81]. A recent application is the production of biopolymers[6], which resulted in a higher molecular weight bio-polymer in comparison to the batch reactor. The effect of inefficient chain propagation as a result of diffusion limitation in the batch reactor was eliminated in the microreactor.

Microreactors are a promising class of reactors for a transition from traditional reactor modules to continuous flow reactors for industrial manufacturing. Some of the key challenges[67] that need to be addressed are (i) clogging of channels with particles and slurries to ensure stable operating conditions, (ii) lack of computational tools and adequate information of reaction mechanisms for achieving a better control over process optimization in the reactor and (iii) difficulty in implementing "plug and play" reactor configuration as the reactor design is not universal. Currently, the production scale-up of low cost chemicals in a microreactor is not economically viable, but the operation cost is justified for high value chemicals as the enzymes are recycled, and so they can be considered as a potential opportunity by industry. The future scope for the reactor lies in engineering continuous and sustainable processes by improving existing protocols for multistep reactions, accurate reaction control to further enhance the selectivity of the reactor, reducing the reactor design time and cost by using active screening parameters (temperature, pH, substrate concentration, etc.) and application to multiphase reactions that are usually limited by low conversion and rapid enzyme deactivation.

11.3.2.3 Immobilized Monolithic Enzyme Reactors (IMERs)

Monoliths are structural supports, comprising of well-defined capillary channels. The enzyme is immobilized by either wash or dip coating on the inner walls of the monolith, aiming to retain the porosity of the support and achieving a high enzyme activity (Figure 11.4).

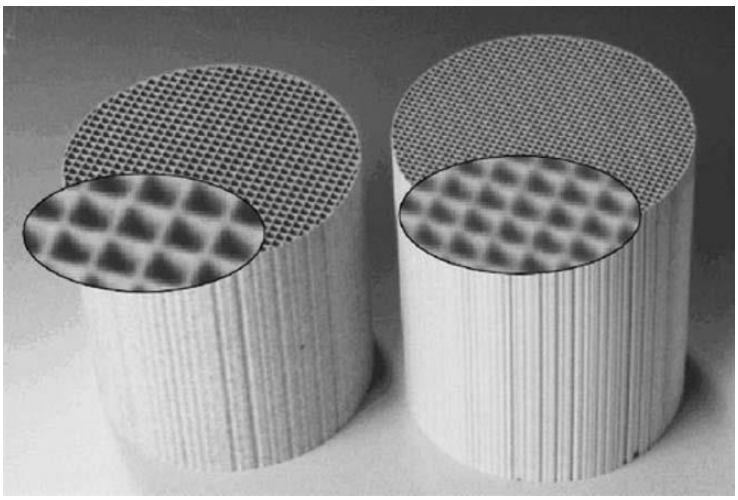

Figure 11.4 Monolithic supports for enzyme immobilization. Reprinted from Lathouder et.al

Traditionally, monolith catalytic reactors have been used for emission control from automobiles. However, their application is becoming more diverse and they are now widely applied in the chemical and biochemical industries owing to the range of advantages of these reactors[10, 82]:

- One of the main features is the reduction in pressure drop by a couple of orders of magnitude when compared to the PBRs.
- A higher surface area, 1.5 to 4 times higher than reactors with catalyst pellets, which results in enhanced reaction rate and conversion.
- The catalyst efficiency is improved due to the shorter diffusion channels and a reduction in the mass transfer resistance. Reaction selectivity is also improved as it is easier to control the reactions.

- They also facilitate process miniaturization as they can be portable and help in mobile applications like ethanol reforming and cleaning of aircraft cabins. Development of small monolithic reactors also find application in fast screening of drugs in pharmaceutical industries.

Monolithic supports can be either be organic polymers or inorganic monoliths. Organic monoliths are more popular as they are stable over a wide range of operating conditions, and have abundant functional groups, which facilitate efficient and simple enzyme immobilization protocol, and are also biocompatible. The use of epoxide groups (with or without modification) in a monolith for enzyme immobilization has been well reported in literature[83-85]. The enzymes retained their activity for a longer period, accompanied by a lower pressure drop, compared to the PBR. Monolithic Convective Interaction Media (CIM discs) are commercially available monoliths (BIA separation) and have also been used for enzyme immobilization[86, 87]. Silica-based monoliths are the most popular inorganic support for enzyme immobilization as they offer a macroporous channel and mesoporous skeleton, which enable higher enzyme loading, fast mass transfer and lower pressure drop[88]. Composites[89], modified silica[90, 91] and sol-gel[92] networks are other monoliths, which have been used for enzyme immobilization. In all cases, enzyme activity was retained over a longer time period, due to the inherent structural stability provided by the monolith.

Application of IMER for production of biodiesel has been reported in literature using both inorganic and organic monoliths. Silica[93] and acrylic[86] based IMER have been used for enzymatic transesterification of oil, resulting in high product yield and selectivity compared to the free enzyme catalyzed reaction. IMERs have also been used in chemical synthesis. Terpene was synthesized using lipase immobilized on a styrene based monolith, and it out-performed the PBR[94]. Another successful application was the production of lactose-free milk using β-galactosidase immobilized on lab-made agarose column[95]. Use of IMERs in

pharmaceutics has also shown to provide the advantage of fast screening of drug molecules and drug development, and since the majority of the targets are enzymatic in nature, the enzyme immobilized monoliths can alleviate the need for complex in vitro characterization tests. CIM based IMERs immobilized with acetylcholinesterase have been extensively used in the therapeutic research for Alzheimer's disease[96, 97]. The advantage with the IMER was that it provided the necessary structural stability for the enzyme, and over 2000 individual tests could be carried out without a loss in the enzymatic activity. Finally, a widely reported application of IMERs is the digestion of proteins by enzymes. Compared to the conventional time consuming in-solution digestion, IMERs facilitate protein digestion within a few minutes, and also allow automation as they can be integrated within the system. Immobilized trypsin has for example been used for the digestion of cytochrome[85], BSA[98] and peptides[99]. Hybrid organo-inorganic monolith has been used for automated digestion of insulin and lysozyme[75].

Despite the number of advantages associated with IMERs, the technology is still novel and has not been employed for large scale industrial bioprocesses[82, 100]. The monoliths are currently lab made, tailored for a specific enzyme and the scale-up of monolith production is a challenge in itself. The cost of manufacturing monolithic catalysts is higher than pelleted catalysts. However, the industries should consider the re-usability of monoliths, which can offset the high initial cost. Irreversible immobilization of enzymes on expensive monolithic supports hinders their re-usability once the enzyme deactivates and regeneration of such supports have to be considered.

11.3.2.4 Rotating Packed Bed Reactors

Rotating packed bed reactors (RPB) have been studied since the 1970s and facilitate intensified heat and mass transfer reactions generally applied for gas-liquid phase reactions.

The application of the RPB reactor for enzymatic reactions was developed in the mid-90s and is still not well researched. They can be thought of as a combination of a rotor-stator and a static mixer in which the centrifugal force causes the fluids flowing through the packed bed immobilized with enzyme to spread out as fine droplets or thin films, thus resulting in better mixing (Figure 11.5).

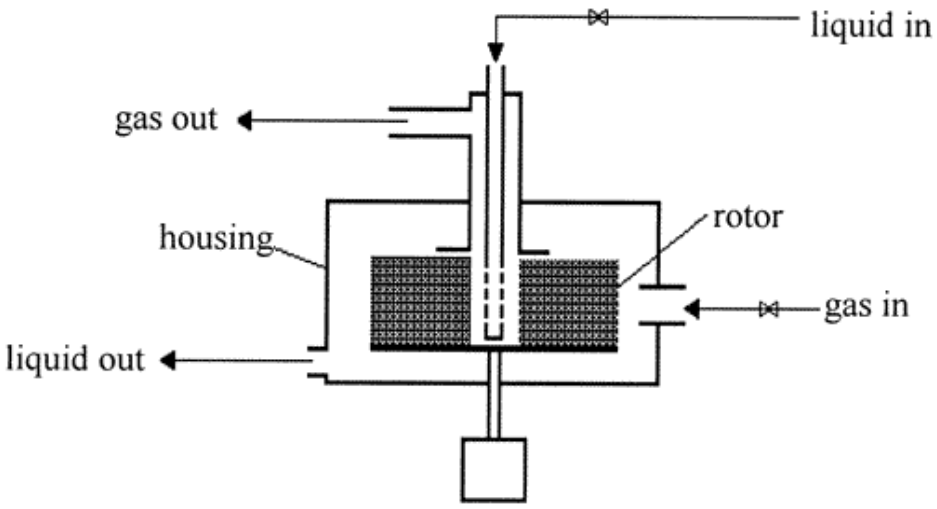

Figure 11.5 Schematic diagram of a rotating packed bed reactor. Reprinted (adapted) with permission from Liu et.al © 1996 American Chemical Society.

Some of the characteristics of the RPB are as follows [101]:

- Mass transfer resistances are reduced due to the centrifugal force causing the formation of a thin film completely wetting the packed enzyme bed.
- The residence time of the RPB is in the order of 10 to 100 μs enabling them to be employed for fast reactions.
- Enzymes activity is retained over a longer period as they are protected from the hydrodynamic forces within the reactor.

The RPBs have to date been used for nanofabrication[102, 103], advanced oxidation[104, 105] and biodiesel production[106]. More recently, the RPBs have been extended for enzymatic biotransformation reactions[107-109] like glucose oxidation and oil hydrolysis. For example, the importance of rotational speed was demonstrated by a 20% increase in production rate with increasing speed for glucose oxidation[107]. The RPB has also been successfully employed for a three phase reaction system, which proved to be more efficient than a conventional fluidized bed reactor in terms of energy efficiency and reducing the attrition of the immobilized catalyst particles. Enzymatic conversion of *rifamysin B* to *rifamycin S*, an inflammatory drug, proceeded faster than in the RPB[108]. The efficiency of the degumming of rice bran oil using immobilized *Lecitase*[109] was increased with the impeller speed retaining the enzymatic activity.

The application of RPB to enzymatic reactions is still limited. Reactor scale-up requires an increase in the packed bed size, leading to reduced reactor efficiency due to incomplete wetting of the packing. The energy and maintenance costs of the rotating system are currently higher than conventional columns, which can be offset by a reduction in the size and the capital cost of the reactor. The future prospects for the reactor are in terms of advances in design and process control for continuous reactions and extension into more complex enzyme catalyzed reactions.

11.3.2.5 Spinning Mesh Disc Reactor (SMDR)

The Spinning Mesh Disc Reactor (SMDR) is an innovative reactor design developed by the author. Like the spinning disc reactor (SDR) technology, the SMDR also uses centrifugal force for an even spread of thin film on the surface of the disc, but additionally holds a cloth immobilized with the enzyme (Figure 11.6). The cloth is a critical component as it allows for improved mixing on top as well as within the cloth, which increases the contact between the

enzyme and the reactants[27], and thus, creating a highly localized reaction zone. The key advantages of the SMDR are[27, 67]:

- Reaction intensification occurs through a combination of increased mass transfer and interfacial surface area.
- The cloth protects the enzymes from hydrodynamic forces and the enzyme activity is retained over multiple cycles.
- The residence time is in the order of milliseconds, which facilitates fast reactions.
- Mild operating conditions allow for reactions in aqueous and organic solvent medium.

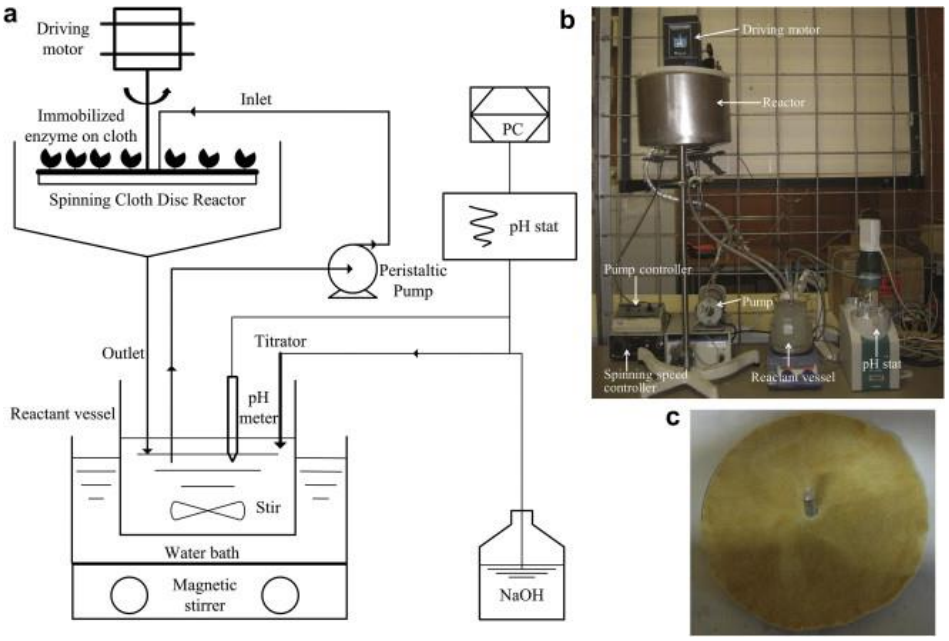

Figure 11.6 (a) Schematic diagram of the SMDR for tributyrin hydrolysis, (b) Photograph of the reactor set-up, (c) Enzyme immobilised on a woollen cloth support. Reprinted from Feng et.al © 2013, with permission from Elsevier

The SMDR has been used to study the hydrolysis of tributyrin using free and immobilized lipase on wool[27]. In both cases, the reaction conversion was higher than the BSTR. The reaction conversion also increased with the increase in spinning speed up to a certain

threshold, beyond which enzyme leakage was observed, likely due to the surface shear on the cloth surface. The enzyme cloth was re-used for 15 cycles and 80% of the original activity was retained, demonstrating the robustness of the reactor. It has also been shown that any cloth support used for enzyme immobilization can be incorporated in the SMDR, paving way for different structural supports to be integrated with this technology. The improved mixing in the SMDR can be attributed to the number of tanks in series, which is two times lower than reactor without the cloth. Scale-up of the SMDR can be achieved by increasing the number of immobilized cloths and numbering up of the discs[22]. Similar to the scale-up of microreactors, scale-up of a SMDR in general does not require a re-design in terms of operating co-efficient like Prandtl and Reynold's numbers, but is solely governed by physical laws[66]. The reactor has recently been extended to chemical synthesis, producing nitroalcohol from aldehydes[100].

Due to the recent development of the SMDR, there has not been a technology transfer to the industry. The SMDR is as a niche and flexible technology, suitable for the production of pharmaceuticals and fine-chemicals. Future research should focus on extending the SMDR technology to organic synthesis, cascade and multifunctional reactions by integrating alternate forms of energy. Parallel operation of multi-disc design can also be one of the ways to achieve the production demand.

11.4 Conclusion

Process intensified enzyme reactors have been successful in surpassing the performance of conventional reactors for biotransformation on a lab scale, justifying the academic and industrial attention they have received in the last decade. Reactor engineering coupled with a fundamental understanding of the chemistry has resulted in improved efficiency of enzyme reactions developing a range of PI-ERs. While membrane and micro reactors have been tested for a range of applications, RPB and SMDR have the potential versatility to transform

novel, bench scale chemistry into continuous processes. The future scope lies in integration of PI domains in the form of alternate energy source, multi-functionality and synergistic reactions. The next steps for industrial implementation of these technologies also include cost assessment, process control, design and development of the reactors for higher throughput. Another possible means of ensuring faster technology transfer to industries is by commercialization of PI-ER research as spin-out companies. To conclude, the combination of process intensification and enzyme catalysis is an effective way of achieving sustainable processes on an industrial scale, and this can only be achieved if engineers and chemists work together at all the development stages, rather than as an afterthought.

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