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Production of Microbial Enzymes by Solid-state Fermentation for Food Applications

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1. Introduction

Many studies have been published in recent years supporting the application of Solid-State Fermentation (SSF) in valorization of agricultural byproducts and in production of fine chemicals and enzymes. Solid-state processes are, therefore, of special economic interest for countries with an abundance of biomass and agro-industrial residues, as these can be used as cheap raw materials (Gombert et al., 1999; De la Cruz Quiroz et al., 2015). In addition to the feasibility of the process, SSF has several advantages concerning molecules production, especially enzymes, over submerged fermentation (SmF) (Panda et al., 2016). Indeed, numerous studies based on multiple hydrolases of industrial interest show the quantitative and qualitative advantages of SSF-produced enzymes over those produced by SmF (Acuña-Argüelles et al., 1995; Barrios-González, 2012). Indeed, hydrolases – EC 3 – represent the main group of enzymes used in the

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industry; they function without requiring the addition of cofactors and are massively secreted by filamentous fungi under certain conditions, as they feed on complex polymeric substrate. Concerning the differences in SSF and SmF, they originate due to the fact that the type of culture depends on complex physiological interactions between the microorganisms and the medium occurring during fermentation (Pandey, 2003). These differences occur at multiple levels—from the physical aspect of the microorganisms to its genetic regulation (Marzluf, 1997).

In this chapter, we briefly focus on SSF strategies for production of vital enzymes required for food applications.

2. World Demand for Enzymes

Enzyme technology is an interdisciplinary field recognized by the Organization for Economic Cooperation and Development (OECD) as an important component of sustainable industrial development. Its applications range from straightforward industrial processes to pharmaceutical discovery and development. Thus industrial enzymes represent the heart of biotechnology (Thomas et al., 2013). The world market for industrial enzymes was estimated at US$ 625–700 million for 1989–1990. More recently it was estimated at US$ 3,3 billion in 2010 and was expected to reach US$ 4,4 billion by 2015 (Jaramillo et al., 2015). Amongst the various industrial sectors, 75 per cent of the industrial enzymes are hydrolases (Bhat, 2000). Proteases constitute one of the important groups accounting for about 60 per cent of the total enzyme utilization (Sawant and Nagendran, 2014). Cellulases account for approximately 20 per cent (Juwaied et al., 2011) while lipases account for one per cent (Mala and Takeuchi, 2008).

During the early stages, commercial use of enzymes in the food industry was limited to a small number of applications, such as production of fermented food products upon the action of endogenous proteases under appropriate conditions. Today, enzymatic methods constitute an important and essential part of the processes used by the modern food industries to produce a large and diversified range of products for human consumption (Shahidi and Kamil, 2001). In 2010, the global enzyme market was dominated by the food and beverage industry, which has benefitted with the expansion of the middle class in rapidly developing economies. Indeed, consumer demand requires higher levels of quality in food in terms of natural flavor, taste, digestibility and nutritional value not only in the US and Europe, but also in the developing countries where consumption shifts away from staple sources of calories towards more demanding requirements. This trend triggered the need for development of enzymes applications in food processing. In the world enzyme market, food industry comes before household care, animal food and bioenergy, and is expected to continue its growth (Li et al., 2012; Miguel et al., 2013).

3. Solid State Fermentation (SSF)

Throughout history, enzyme technology is notably linked to development in the fermentation field. As a consequence, just like enzyme technology, SSF is a very ancient process primarily used to meet human needs. Typical examples of it are fermentation

of rice by *Aspergillus oryzae* to initiate the koji process and *Penicillium roquefortii* for cheese production. In China, SSF has been used extensively to produce brewed food (Rodrìguez Coute and Sanromán, 2006); nowadays, SSF is widely used in the entire fermentation industry, particularly for the production of enzymes for which it holds tremendous potential (Pandey et al., 1999). SSF is a process involving microbial growth on the surface and inside a porous matrix in the absence or near-absence of free liquid in the inter-particle volume (Lonsane et al., 1985; Hesseltine, 1987; Raghavarao et al., 2003). The low moisture content means that fermentation can only be carried out by a limited number of microorganisms, mainly yeasts and fungi, although some bacteria have also been used (Rodrìguez Coute and Sanromán, 2006). In addition, concerning the inoculation, spores are usually preferred over vegetative or mycelial cells in the SSF system due to the ease in mixing the inoculum with autoclaved moist solids (Roussos et al., 1991). Even though the free liquid runoff is very limited, water is one the most important factors to consider (Oriol et al., 1988). It is indeed essential for microbial growth to occur and its role in biological systems are numerous. It allows, for example, stability and function of the biological structures organized at the molecular and cellular levels. In addition, solutes as well as dissolved-gas transfers take place in the aqueous film surrounding the microorganisms. So, even in SSFs, the microorganisms are in a liquid medium (Graminha et al., 2008). Indeed, solute diffusion in the substrate must occur in the liquid phase and gaseous diffusion in the substrate can occur in the liquid as well as in the gaseous phase (Gervais and Molin, 2003). In the near-absence of free running water, its presence depends only on the water-retention abilities of the medium (Manpreet et al., 2005). The osmotic gradient due to heterogeneous distribution of solutes and adsorption forces can be recognized as key factors in SSF. More specifically, the low level of water activity (a_w) of the solid substrate has a significant effect on the physiological activity of microorganisms and enzyme production (Antier et al., 1993).

The medium is also an important factor to be taken into account following two considerations—as substrate, it has to efficiently cater to microbial nutritional needs and as a support of the culture, it has to possess favorable physical properties (Pandey et al., 2000). Smaller substrate particles provide larger surface area for microbial attack and, thus, are a desirable factor. However, too small substrate particles may result in substrate accumulation, which may interfere with gaseous exchanges and hence in microbial respiration. Therefore, the result is poor growth. In contrast, larger particles provide better medium aeration efficiency due to increased inter-particle space, but provide limited surface for microbial attack. This necessitates a compromised particle size for a particular process (Pandey et al., 1999; Guan et al., 2014). Following the same logic, if the moisture content is too high, the void spaces in the solid are filled with water, resulting in oxygen limitation. On the other extreme, if the moisture content is too low, microorganism growth will be hindered (Vitcosque et al., 2012).

There is a distinction between the two types of medium used in SSF:

- It can be synthetic and work as a support only. Therefore it must be complemented with nutritive substances or
- Be of natural origin, working both as support and substrate and in this case, it's not an obligation for it to be complemented with nutritive supplements

Generally, SSF uses natural products – typically starch or ligno-cellulose-based agricultural products, which may have a disadvantage. The carbon source constitutes part of their structure. During the growth of the microorganisms, the solid medium is degraded and as a result, the geometric and physical characteristics of the medium change. Consequently, heat and mass transfer can be reduced (Ooijkaas et al., 2000). Mass transfer includes nutrient consumption and gaseous exchanges. Most of the processes being aerobic, the limitation of oxygen after its uptake during the exponential phase may limit the growth at the industrial scale if the gaseous phase inside the inter-particle void is not regenerated (Rajagopalan and Modak, 1995).

Concerning the heat transfer, a large amount of metabolic heat is generated during SSF and its rate is directly proportional to the level of metabolic activity in the system (Liu, 2013). Heat transfer in SSF reactors is not as efficient as in SmF, mainly due to the solidness of the substrate—the solid matrix has a low heat conductivity—and the lack of free water available during fermentation, since the thermal conductivity of air is very poor compared to water (Jou and Lo, 2011; Robinson and Nigam, 2003). As a consequence, heat removal is one of the major constraints in SSF, especially in large-scale processes (Figueroa-Montero et al., 2011). Numerous strategies to overcome this issue have been adopted, from which a wide diversity of bioreactor designs have emerged: static or stirred, aerated or not (Roussos et al., 1993; Durand, 2003). Finally, using a complex medium, SSF processes rarely yield to purified compounds; instead molecule extraction yields crude complexes. In the case of industrial utilization, its particularity not a drawback: indeed, industrial utilization of purified enzymes is not economically justified. In this case, the use of a crude enzyme is most adequate, bearing in mind the obviously lower commercial value for industrial use. The effective dosage of crude enzyme costs about one per cent of the cost of pure enzymes (Leite et al., 2008).

Some common enzymes used in the food industry and produced under SSF are given in Table 1.

4. Comparison Between SSF and SmF

In order to fully understand the strong points of this process, it is useful to compare SSF with its liquid equivalent. The advantages are based on two main aspects—first, an economical aspect using agricultural byproducts, which are naturally rich in carbohydrates and other nutrients and produced in excess all over the world, as the culture medium in SSF is cheaper than using the synthetic liquid substrate (Rodrìguez Coute and Sanromán, 2006; Balkan and Ertan, 2007). Some of the substrates include sugarcane bagasse, wheat bran, rice bran, maize bran, gram bran, wheat straw, rice straw, rice husk, soy hull, corncobs, banana waste, tea waste, cassava waste, apple pomace, etc. to name only a few. Wheat bran, however, is the most commonly used substrate (Sangeetha et al., 2004). Moreover, the absence of free water reduces liquid volume used for the process and the downstream effluent treatment costs (Ghosh et al., 2013). Economic analysis of the production of lipase by *Penicillium restrictum* in SSF and SmF cultures showed that the investment capital necessary for SmF was 78 per cent higher than that required for SSF. Consequently, the price of the SSF product was

Table 1. Some example microbial enzymes commonly used in food processing produced by SSF.

Enzyme	Food Industries	Microorganism	By-products	References
Amylase	Sugar industry	*Penicillium chrysogenum*	Corncob leaf, rye straw, ye straw, wheat bran	Balkan and Ertan (2007)
B-galactosidase	Milk industry	*Aspergillus oryzae*	Wheat bran and rice husk	Nizamuddin et al. (2008)
Cellulase	Wine and brewery industry, fruit and vegetables juice	*Trichoderma reesei* *Trichoderma viride* *Pleurotus* sp. *Aspergillus awamori* *Aspergillus niger*	Wheat bran Sugar cane bagass Banana wastes (leaf biomass and pseudostems) Grape pomace Kitchen waste residues (corn cobs, carrot peelings, composite, grass, leaves, orange peelings, pineapple peelings, potato peelings, rice husk, sugarcane baggage, saw dust, wheat bran, wheat straw)	Singhania et al. (2007) Juwaied et al. (2011) Reddy et al. (2003) Botella et al. (2005) Bansal et al. (2012)
Chitinase	Food preservatives	*Beauveria bassiana* *Metarhizium anisopliae* *Aspergillus terreus*	Prawn waste Silkworm chrysalis Parrot fish scales waste	Suresh and Chandrasekaran (1998) Barbosa Rustiguel et al. (2012) Ghanem et al. (2013)
Fructosyl transferase	Prebiotic	*Aspergillus oryzae* *Bacillus subtilis*	Rice bran, wheat bran Starch	Sangeetha et al. (2004) (Esawy et al. (2013)
Lipases	Food additives	*Penicillium restrictum*	Babassu oil cake	Gombert et al. (1999)
Pectinase	Wine and brewery industry, fruit and vegetables juice, oil	*Aspergillus niger*	Coffee pulp Wheat bran and soy bran	Antier et al. (1993) Castilho et al. (2000)
Protease	Fruit and vegetables juice, coffee extraction	*Aspergillus oryzae* *Pleurotus ostreatus* and *Trametes versicolor* *Aspergillus oryzae*	De-oiled seedcakes from *Jatropha curcas* Tomato pomace Canola Cake	Thanapimmetha et al. (2012) Iandolo et al. (2011) Freitas et al. (2013)
Rennet	Cheese industry	*Mucor miehei*	Complemented wheat bran	Thakur et al. (1990)
Xylanase	Fruit and vegetables juice, coffee extraction	*Aspergillus niger* *Scytalidium thermophilum*	De-oiled seedcakes from *Jatropha curcas*	Ncube et al. (2012) Joshi and Khare (2011)

47 per cent lower. The investment return from the SSF process can reach 68 per cent within five years (Graminha et al., 2008). This economical advantage also induces an important concept: valorization. Indeed, the agricultural industry produces important amounts of byproducts whose main part is unused and raises environmental issues (Arumugam et al., 2014). SSF allows the production of value-added molecules from unused resources, thus decreasing the pollution volume and its toxicity, as is the case of *Jatropha curcas* byproducts. The seeds of this plant contain high amounts of oil containing triglycerides which, after certain treatments, including transesterification, lead to the formation of biodiesel (Mazumdar et al., 2013). The byproduct is a de-oiled seedcake which is highly toxic due to the presence of phorbol esters and other anti-nutrients. If, left to decay, its accumulation would lead to environmental problems. However, its composition – 60 per cent protein, 0,6 per cent fat, 9 per cent ash, 4 per cent fiber and 26 per cent carbohydrates – makes its utilization with the right strain suitable for numerous SSF processes (Joshi and Khare, 2011; Kumar and Kanwar, 2012; Ncube et al., 2012; Thanapimmetha et al., 2012). The second main advantage of SSF concerns qualitative and quantitative aspects of production of valuable molecules. Indeed, it has been shown that certain molecules produced under SSF often have different and more interesting properties than the ones obtained with SmF. Some of them includes, for example, more thermostable or show higher pH stability (Mateos-Diaz et al., 2006; Mienda et al., 2011; Barrios-González, 2012; Saqib et al., 2012). In their study, Acuña-Argüelles et al. (1995) produced pectinases with both SSF and Smf. According to the electrophoretic patterns of proteins, the culture method appeared to induce differences in the mobility of pectinases, besides variations between the substrate affinities (K_m) for some pectinases. They explained that this difference is related to the various levels of glycosylation – the attachment of the sugar molecule oligosaccharide, known as glycan, to an amide nitrogen atom of a protein – induced by the cultural method, which changed pectinolytic activities and also thermostability. Later studies show that glycosylation could improve the protein thermostability (Zhu et al., 2014). The yields are higher as well. But it is true for a majority of molecules in enzymes that a greater quantity of fungal exoenzymes accumulated when the growth occurred under SSF than under SmF (Hernandez et al., 1992; Kar et al., 2013). This may be explained by the fact that the same observation can be made concerning the fungal biomass, which is remarkably higher, during the same incubation time, when produced by SSF. The morphological difference between biofilm and pellet growth indicates difference in physical structure and also implies dissimilar mass transfer patterns. Indeed, by comparing the area to volume ratio, it appears that SSF cultures have a much larger air to liquid interphase than conventional SmF pellets and are thus more likely exposed to passive gas exchanges (Viniegra-González et al., 2003). Furthermore, some studies have highlighted the variation of proteome, indicating a differential gene expression ruled by physical interactions between the fungus and its support (Gamarra et al., 2010). It has also been shown that SSF reduces the level of catabolite repression or end-product feedback repression compared to the SmF system; yet the exact reason is not fully understood. This is cost-effective over liquid fermentation, which needs to use lower substrate concentrations in the fermentation media or use cost-intensive fermentation operation strategies in order to overcome catabolite repression (Nandakumar et al., 1999). For example, in a homogeneous liquid

medium, *Aspergillus niger*'s endo- and exopectinases' synthesis is repressed if the medium contains glucose (3 per cent). Conversely, in SSF endo- and exopectinases' synthesis is not affected for a medium much richer in glucose (upto 10 per cent). Pectinases' activities even increase when pectin is added to the medium (Solís-Pereira et al., 1993).

5. Bioreactors

As said before, in bioreactor models, the two most important environmental variables are temperature and water activity of the bed and both of them are intimately tied to the metabolic activity of the microorganism. Generally, literature describes many kinds of SSF bioreactors, depending on whether air is forcefully blown into the bed and/or the substrate is agitated: some of them include tray, packed bed, rotating drum, gas–solid fluidized bed, stirred aerated bed, and rocking drum bioreactors (Jou and Lo, 2011). Furthermore, as an endothermic process, water evaporation is really an efficient method to overcome heat generation. Thus aeration with water-saturated air may be used to avoid dryness in the cultural medium and regulate the heat generated during the growth (Saucedo-Castañeda, 1994; Utpat et al., 2014). With regard to mixing three strategies are available: the substrate bed may either be left static or mixed only very infrequently or it might be mixed reasonably frequently with static periods in between, or alternatively it might be mixed continuously (Mitchell et al., 2000). Each of them has been successfully used to produce enzymes.

The first categories of bioreactors are referred as static bioreactors as they are mixed only very infrequently – once or twice a day. The tray bioreactor, also known as koji bioreactor, is the most widely used bioreactor for SSF. It also has the simplest design: it consists of substrate placed on a tray placed in a room where atmosphere is controlled (Rosales et al., 2007; Brijwani et al., 2010). As there is no forced aeration in the medium, mass and heat transfers occur by natural diffusion and convection. Therefore, the substrate thickness on the tray is the major limitation parameter (Figueroa-Montero et al., 2011).

Rodrìguez Coute et al. (2003) have shown that on barley bran as medium, the tray configuration led to the highest laccase activity when compared to packed-bed bioreactor. However, for a better monitoring, other bioreactors may be used. In addition, Raghavarao et al. (1993) determined the critical height of substrate on a perforated bottom tray as 4.78 cm; over this height, the oxygen concentration may fall to zero during fermentation. Such a value suggests that an important surface must be used in order to achieve industrial-scale production when using this technique. The packed-bed has advantages over the tray because the forced aeration allows better control of environmental conditions in the bed, due to the ability to manipulate the temperature and flow rate of the process air (Mitchell and von Meien, 2000). Glass columns, also known as 'Raimbault column', are the typical packed-bed bioreactor at laboratory scale (Rodríguez-León et al., 2013). They have a perforated base plate on the bottom which allows the air flow and can be oriented vertically or horizontally. Castro et al. (2015), in order to overcome the scale-up limitations of conventional tray-type bioreactors, used a cylindrical fixed-bed bioreactor with forced aeration – with a working volume

of 1,8 l – for the production of a pool of industrially relevant enzymes by *Aspergillus awamori*, using babassu cake as the raw material. They reported that despite significant temperature gradients, it was possible to obtain good titers with production of the six enzyme groups evaluated: exo-amylases, endo-amylases, proteases, xylanases and cellulases.

Another category consists of bioreactors in which the bed is continuously mixed or mixed intermittently with a frequency of minutes to hours and air is circulated around the bed, but not blown forcefully through it. Two bioreactors that have this mode of operation, using different mechanisms to achieve the agitation, are 'rotating drum bioreactors' and 'stirred drum bioreactors'. In rotating drum bioreactors, the drum is partially filled with a bed of substrate and the whole drum rotates around its central axis to mix the bed. In stirred drums, the bioreactor body remains stationary with paddles or scrapers mounted on a shaft running along the central axis of the bioreactor rotating within the drum (Mitchell et al., 2006). Such bioreactors increase mass and heat transfers by improving homogeneity of the bed, using agitation of the medium. This kind of a process is relevant only if the fermentation is carried with a microorganism resistant to damages from the shear forces caused by agitation and able to grow on a substrate with lower porosity after compaction of the medium (Fujian et al., 2002). Typically, fungi with non-septate hyphae – like zygomycetes – are less resistant to agitation (Durand, 2003). This issue may be overcome if the mixing periods are relatively short, as in the case of intermittently mixed bioreactors, since many fungal processes can tolerate infrequent mixing (von Meien et al., 2004).

The last category includes bioreactors with both aeration and agitation inside. The agitated bioreactor is generally preferred on an industrial scale because it maximizes the mass and heat transfers. A forcefully aerated and intermittently mixed rotating-drum bioreactor, named *FERMSOSTAT*, utilizing the following agitation parameters—5 minutes of agitation at 0.5 rotation per minute every day—showed promising results in the production of cellulases (Lee et al., 2011). This category also includes the gas-solid fluidized bed, in which solid substrate is placed on a porous plate or metal net and sterilized air is blown in under the plate. When the airflow rate is high enough, solid substrate particles get suspended in the gas phase, allowing a very good rate of heat and mass transfer (Cen and Xia, 1999). Amylases and proteases produced from *Eupenicillium javanicum* under fluidized culture were reported to have activities two times higher than that obtained in a stationary culture (Tanaka et al., 1986). However fluidization requires the use of fine particles and the minimum air velocity for fluidization is high in high-power requirements. Therefore, large, coarse and sometimes sticky particles, which usually appear in SSF are difficult to fluidize. A spouted bed requires a lower gas-flow rate and may provide good mass and heat transfer for solid materials that are too coarse or dense for stable fluidization (Wang and Yang, 2007). Silva and Yang (1998) have shown that amylase activities from *A. oryzae* grown on rice were equivalent when a packed bed bioreactor and gas-solid spouted-bed bioreactor with intermittent spouting of air were used and these activities were higher than those obtained in a tray-type reactor. However, the fermented rice obtained from the gas-solid spouted-bed bioreactor was homogeneously fermented and did not show rice aggregates knitted together with fungal mycelia, as in the packed bed bioreactor.

Continuous SSF also exists. In this case, the solid phase within the bioreactor can be assimilated to a flow wherein there is no heat and gaseous gradient. However, there are specific challenges to operate continuous SSF bioreactors and this process is currently scarcely used in the industry. Consequently, batch production is more common (Ramos Sánchez et al., 2015).

6. Techno-economic Feasibility of Enzyme Production in SSF and Limitations

Despite all these advantages – the biggest one being enzymes produced in higher levels in SSF – SmF remains, in the vast majority of cases, the preferable method to produce molecules on an industrial scale (Mitchell et al., 2006). Indeed, SSF is still suffering from lack of industrial-scale bioreactors (Farias et al., 2015; Ramos Sánchez et al., 2015). SSF up-scaling, necessary for use on an industrial scale, raises severe engineering problems due to the build up of temperature, pH, oxygen, substrate and moisture gradients (Hölker et al., 2004). On the contrary, in SmF, the media is made up essentially of water. In this environment, the temperature and pH regulation are trivial and pose no problem during the scaling-up of the process. The only one major difficulty encountered is the transfer of oxygen to the microorganisms; this can easily be overcome on an industrial scale with an adapted shape of the bioreactor and the presence of an agitation/aeration system, while in the SSF, the system is multiphasic and thus more complex. So, above some critical quantity of substrate, the metabolic heat removal becomes difficult to solve and restricts the design strategies that are available. The solid medium becomes compacted or creates air channeling, leading to a system with inefficient heat and mass transfers (Durand, 2003).

Various possibilities may be explored to overcome the problems encountered during the up-scaling of the process, like increasing the dimensions of the bioreactor. In this case, the most adapted process is forced aeration combined with agitation. Indeed, aeration efficiently removes metabolic heat with water evaporation and the agitation in association with sprayed water maintains the water activity homogeneous everywhere in the substrate. However, as dimensions increase, maintaining asepsis for efficiency of the process – sterilization being a process that requires important handling – may be difficult. Another possibility is to reduce the maintenance operations as it is the case for the *FMS-unique* bioreactor, a single-use packed-bed bioreactor which can process 5 kg of dry substrate to autoclave directly inside the bioreactor. In this case, the relatively low quantity of fermented substrate enables aeration to efficiently counterbalance the metabolic heat generation. The small amount of product can also be offset by the number of easily operating bioreactors working in parallel (Roussos et al., 2014).

By the way, examples of industrial production of enzymes using SSF and which are economically competitive do exist. Japan is one of the major actors in this domain. Indeed, it is a very large producer of soya sauce and SSF is an integral part of the sauce production process. Therefore, this particular industry has enabled the country to make technological advances in the field of SSF bioreactors, consequently driving the other industrial SSF processes, such as enzyme production (Suryanarayan, 2003).

7. Conclusion

SSF is successfully employed in enzyme production. The increased production of many induced enzymes using solid-state fermentation is related to a significant resistance of organisms cultivated in a solid medium to catabolic repression (Stoykov et al., 2015). Furthermore, the enzymes produced possess interesting properties, such as thermostability, which can be particularly valuable in various industries (Zamost et al., 1991; Mateos-Diaz et al., 2006). Indeed there is evolution of higher fungi on solid substrates, with a wide majority of these known fungi being terrestrial. As a result, the cultivation of such fungi in an aqueous medium doesn't optimize their metabolism and yield (Hölker et al., 2004). Many studies can be found in literature relating to successful enzyme productions using SSF. However, SmF remains the most widely used process to produce enzyme on larger scales, but as the engineering improvements progress, SSF, driven by environment-friendly and economic considerations, should create a growing enthusiasm in industries to become the next common way to produce enzymes on an industrial level in the future.

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