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Review

Industrial biotransformations in the synthesis of building blocks leading to enantiopure drugs

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ABSTRACT

Due to the growing demand of enantiomerically pure compounds, as well as the increasing strict safety, quality and environmentally requirements of industrial synthetic processes, the development of more sustainable, healthy and economically attractive strategies for the synthesis of chiral biologically active molecules is still an open challenge in the pharmaceutical industry. In this context, the biotransformations field has emerged as a real alternative to traditional synthetic routes, because of the exquisite chemo-, regio- and enantioselectivities commonly displayed by enzymes; thus, biocatalysis is becoming a widespread methodology for the synthesis of chiral compounds, not only at laboratory scale, but also at industrial scale. As hydrolases and oxido-reductases are the most employed enzymes, this review is focused on describing several industrial processes based on the use of these enzymes for obtaining chiral compounds useful for the pharmaceutical industry.

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1. Introduction

The synthesis of optically pure compounds is increasingly in demand in the pharmaceutical, fine chemicals and agroalimentary industries, as it is well established the importance of the chirality on the activity and properties of many compounds. Thus, the development of new processes for the obtaining of chiral molecules is still an open challenge in organic synthesis, and the production of fine chemicals and drugs by biotechnological methodologies is an emerging research field (Nestl et al., 2011). Due to the high chemo-, regio- and enantioselectivities commonly displayed by enzymes, the biotransformations field has acquired more interest for the production of chiral building blocks, as well as biologically active compounds (de Carvalho, 2011), offering the development of more environmentally and economically attractive processes.

In addition, REACH regulation and the environmental restrictions approved by US, Japan and E.U. in the last decade, has opened a great debate in Fine Chemicals Industry about its immediate future. In this way, Green Chemistry philosophy (Anastas and Eghbali, 2010), promoting the industrial use of chemicals obtained from biomass, the use of green solvents and more sustainable industrial processes, is impacting R + D + i industrial research. The key success in developing "greener" industrial processes is the effective integration of catalytic technologies (chemical or enzymatic) into a general organic synthesis scheme.

In this sense, biocatalysis presents many appealing features in the context of Green Chemistry specially for the synthesis of chiral building blocks leading to enantiopure drugs or food additives (Nestl et al., 2011): gentle reaction conditions (physiological pH and temperature, water as the usual reaction medium, although many green solvents can also be used, as we mentioned before) and an environmentally friendly catalyst (an enzyme or a cell) displaying high activities and chemo-, regio- and stereoselectivities in multifunctional molecules. Additionally, the use of biocatalysts generally circumvents the need for functional group activation, therefore avoiding protection and deprotection steps usually required in traditional organic syntheses. These properties affords processes which are shorter, produce less waste and are, therefore, both environmentally and economically smarter than conventional routes.

Nevertheless, although enzymes are very active and selective biocatalysts, for industrial purposes, a very common reason to engineer them is to increase their stability under the reaction conditions (Tao and Kazlaukas, 2011). In fact, reaction conditions can differ dramatically from those present in a cell, demanding high temperatures, extremes of pH, high substrate and product concentrations, oxidants, and organic cosolvents. Sometimes an enzyme must tolerate these conditions for only a few minutes or hours, but in a continuous manufacturing process, an enzyme may need to tolerate them for months. There are many ways to increase robustness of biocatalysts, being their immobilization probably one of the most traditionally studied and used (Hanefeld et al., 2009). On the other hand, the use of molecular enzyme engineering techniques, such as directed

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evolution (Behrens et al., 2011) has enormously contributed to new biocatalysts, able to work efficiently in experimental conditions very different from the "natural" ones, in terms of temperature, pH, presence of organic solvents, etc.

For sure, another aspect that deserves a close attention is scaling up. Moving one process from laboratory to industrial scale is not trivial at all, and must be perfectly optimized (Tufvesson et al., 2010) to solve all the specific problems that can arise. In fact, successful scale-up of a biocatalytic processes requires a good understanding of the interactions between the biocatalyst and the chemical and physical environment in the reactor. However, it is more difficult to control the physical environment during scale-up. Some key aspects to be considered are correct reactor choice (Palomares et al., 2009), pH control, risks of contamination, logistics, real process feeds, and use of GRAS (Generally Regarded As Safe) solvents (Tufvesson et al., 2010).

Thus, this review provides several examples of the use of biocatalysts (mostly hydrolases and oxido-reductases) in the industrial synthesis of pure building blocks and biologically active compounds useful for the pharmaceutical industry. As we mentioned before, there are many examples reported in literature reviewing this processes at lab scale (Faber, 2011), so we will concentrate on those which have been already implemented at (semi)-industrial scale.

2. Hydrolases in the preparation of chiral dugs

Hydrolases, are a broad group of enzymes, classified by the type of chemical bond they are active on (Faber, 2011). In nature, these enzymes display a digestive catalytic activity. However, their catalytic behavior is more heterogeneous, and they can be employed as biocatalysts of many organic transformations. Hydrolases, more particularly lipases, present different advantages over other biocatalysts, as they require no cofactors for its catalytic behavior; they are active not only in aqueous medium but also in organic solvents, allowing the transformations of non-water soluble compounds; furthermore, many of them are commercially available and easy to handle biocatalysts; they commonly display low substrate specificity and, due to the high regio, chemo- and enantioselectivity of hydrolases, the employ of these enzymes has acquired more interest for the production of chiral building blocks and biologically active compounds in last years (de Carvalho, 2011).

Some examples of hydrolases employed at industrial scale are summarized in Table 1, and will be commented according to the type of hydrolase used (see Fig. 1).

2.1. Lipases

Lipases are commonly the biocatalyst of choice for the synthesis of chiral compounds, through the kinetic resolution (KR) of racemic mixtures or the enantioselective enzymatic desymmetrization (EED) of prochiral compounds. Lipases have been successfully employed in these processes, for enantioselective hydrolysis of esters and amides, or for enantioselective transesterification of secondary alcohols and amines, affording the corresponding chiral esters or amides, respectively.

Candida rugosa lipase (also known as *Candida cylindracea* lipase) is one of the most employed serine-hydrolases in organic synthesis. Several industrial processes based on the use of this lipase as catalyst in the preparation of pharmaceuticals are already implemented. One of these examples can be found in the synthesis of non-steroidal anti-inflammatory drugs (NSAIDs), (*S*)-2-arylpropionic acids (active isomer), such as ibuprofen ((*S*)-2-(4-isobutylphenyl)propanoic acid, **(*S*)-1).** The American company Pfizer has developed an industrial procedure for the preparation of (*S*)-ibuprofen (entry 1, Table 1), through the enantioselective hydrolysis of the corresponding racemic methoxyethyl ester catalyzed by *C. rugosa* lipase immobilized in a membrane reactor (Sheldon, 1993). As a slightly acidic medium is required to decrease ibuprofen solubility in order to avoid the inhibition of the enzyme in the presence of an excess of product, the reaction is carried out at 20 °C and pH 5. The main drawback of the process, the low substrate solubility in aqueous medium (below 1 mM) is overcome by the employ of a reactor containing the lipase immobilized in the pores of a membrane, which separates an aqueous-organic solvent biphasic system. The substrate dissolved in the organic phase, is hydrolyzed by the lipase, and the chiral acid product is extracted by the aqueous phase. In a further step, the use of other membrane reactor at higher pH value allows the separation of the chiral (*S*)-ibuprofen from the non-converted substrate.

Lipase from *C. antarctica* is one of the enzymes showing higher versatility in the field of biotransformation. Two iso-enzymes have been described, A (CALA) and B (CALB), which present several differences. CALB shows very low substrate specificity, its catalytic behavior is well known and it has been widely employed as catalyst of many organic transformations. Thus, CALB has been employed by the company Schering–Plough in the desymmetrization of the prochiral diethyl 3-[3́,4́-dichlorophenyl]glutarate to the corresponding (*S*)-monoester, (*S*)-3-(3,4-dichlorophenyl)-5-ethoxy-5-oxopentanoic acid ((***S*)-2)** (entry 2, Table 1), a chiral intermediate for the synthesis of antagonists of tachykinins receptors NK1 and NK2, compounds with potential activity in the treatment of asthma, arthritis and migraine. The enzymatic process has been scaled-up to produce 200 kg of product in 80% isolated yield and an enantiomeric excess higher than 99% (Homann et al., 2001). CALB was also employed as the biocatalyst of the synthesis of the antithrombotic compound Lotrafiban S-16 ((***S*)-3)** described by GlaxoSmithkline Pharmaceuticals (entry 3, Table 1). In this case, CALB is immobilized over a macroporose resine Chirazyme L-2, and catalyzes the enantioselective hydrolysis of the corresponding methyl ester, achieving chiral (*R*)-2-(7-(4,4'-bipiperidine-1-carbonyl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepin-2-yl)acetic acid ((***S*)-3),** at 30 °C in aqueous medium (Walsgrove et al., 2002). The immobilized biocatalyst can be reused, minimizing the cost of the process. The separation of the product is possible just by treatment of the aqueous medium maintained at pH 7.0 with dichloromethane: the acid **(*S*)-3** remains in the aqueous solution, in very high enantiopurity, and the remnant ester substrate is accumulated in the organic phase. Immobilized CALB, Novozyme 435®, has also been described as the most suitable biocatalyst for the preparation of (1*S*,2*R*)-2-(methoxycarbonyl)cyclohex-4-ene-1-carboxylic acid ((**1*S*,2*R*)-4,** entry 4, Table 1), an intermediate for the synthesis of a potential modulator of chemokine receptor activity, by the desymmetrization of the corresponding diester through a stereoselective hydrolysis. The process was optimized and scaled-up to prepare 3.15 kg from 3.42 kg of the diester in two batches (Goswami and Kissick, 2009). It is worth of mention the employ of CALB in the preparation of (*S*)-*terc*-butyl 2-carbamoyl-2,3-dihydro-1*H*-pyrrole-1-carboxylate ((***S*)-5,** entry 5, Table 1), an intermediate in the synthesis of the oral hypoglycemic agent saxagliptin, through the stereoselective ammonolysis of the corresponding ester using ammonium carbamate as ammonia donor to yield 71% of the desired product. The inclusion of calcium chloride and ascarite increased the yield up to 98%, thereby offering an efficient and practical alternative to chemical routes which yield 57–64%. A prep-scale reaction with the process ester feed was used (220 g/L of ester), achieving complete conversion of the substrate, and after workup, the product was isolated in 81% yield and >99% *ee* (Gill and Patel, 2006).

Pseudomonas cepacia lipase has shown to be very selective as catalyst of processes such as hydrolysis of esters or transesterification of secondary alcohols. Paclitaxel (Taxol) is an antimitotic agent, employed in the treatment of different type of cancer as

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