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Communication

Technical–Economic Assessment—The Missing Piece for Increasing the Attractiveness of Applied Biocatalysis in Ester Syntheses?

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Abstract: Although the current literature describes significant advances in biocatalytic ester syntheses, few industrial plants worldwide are currently producing esters using biocatalysts. Green and sustainable esters can be obtained via a biocatalytic route, including some operational advantages over conventional syntheses. An analysis of the literature revealed that most articles neglect or describe the economic issues generically, without quantitative information. Scaling-up studies are also scarce in this field. The main disadvantage of biocatalysis using immobilized lipases—their cost—has not been studied at the same level of depth as other technical aspects. This gap in the literature is less intense in enzymatic biodiesel production studies and, despite the lack of a strict correlation, enzymatic biodiesel commercial plants are relatively more common. Preliminary techno-economic assessments are crucial to identify and circumvent the economic drawbacks of biocatalytic ester syntheses, opening the way to broader application of this technology in a large-scale context.

Keywords: biocatalysis; esters; economic assessment

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1. Introduction

Esters syntheses are technically feasible using biocatalysts in organic media, including many successful examples in solvent-free systems [1,2]. The advantages of biocatalysis in this field include the reduced severity of the processes and the consequent reduction in occupational risks, the increased purity of the obtained esters, and the reduced complexity of downstream operations [1,3,4], with potential positive impacts on economic, social, and environmental parameters.

Considering esters' importance and market size—estimated to reach USD 3 billion in 2027 [1]—it is notable that few companies are currently producing esters catalyzed by lipases. Ansorge-Schumacher and Thum (2013) [3] and Khan and Rathod (2015) [4] mentioned that companies such as Evonik and Eastman were producing esters by biocatalysis at the time they wrote their papers. Years later, the context remains almost unchanged, although the scientific literature and patents in this field have increased drastically. News about the growing interest of big chemical companies, such as Basf, Dow, Clariant, DuPont, and Solvay, in biotechnologies or enzyme production/applications are frequent. However, it is curious that the higher sustainability and product quality obtained from the biocatalytic production of esters seem not so attractive to the chemical industry context.

The question is always surrounding the high cost of the biocatalysts for ester syntheses—immobilized lipases. However, some industrial biodiesel plants are becoming viable (at least on a pilot-scale), and the biodiesel price needs to meet the market demand, which means a low-cost product and a high volume of production [5,6]. Instead, there is an opposite scenario for other esters, with a high price and a low volume demand compared to the fuels market [7,8]. Currently, the chemical route involves using sulfuric acid or *p*-toluene sulfonic acid as catalysts, which are cheap raw materials, contrarily to commercial immobilized lipases available in the market [4,5,9–11]. In terms of operational issues, immobilized lipases also have some advantages compared to conventional catalysts, particularly due to their easy separation from the reaction media (heterogeneous catalysis), the possibility of reusing the biocatalysts, the prevention of corrosion, and their high specificity in esterification [4,10–12]. However, even these advantages are overshadowed by the high costs and the lack of specific studies to address these issues from an economic perspective. Futhermore, life-cycle assessments (LCA) on the current technology for esters syntheses can reveal more clearly the carbon footprints and environmental impacts involved in their production, which may become relevant business issues in the future [13–16].

The technical aspects of biocatalysis applied to esters have been explored in depth over the past two decades. However, the economic issues involved are usually ignored or mentioned generically. Thus, advances in the knowledge of solvent-free esterifications or using green solvents, unconventional reaction media, immobilization techniques for lipases, and the use of agroindustrial wastes to produce lipases or their immobilization supports, among others, are generally discussed only in technical terms. Crucial questions such as the enzymatic activity versus their production costs or the biocatalyst loading required for a given reaction in terms of reuse capacity are commonly neglected in the literature.

This communication article aimed to show a brief survey of the literature to illustrate this problem, some insights to overcome these drawbacks, and future perspectives.

2. Discussion

2.1. Bibliometric Survey on the Economic Assessment of Enzymatic Esterification

A non-extensive survey on the Web of Science database revealed 3196 articles published since 2000 that dealt with enzymatic esterification (including review articles). The number of publications on this topic per year is growing, as seen in Figure 1. However, when economic terms were included in the survey, only 53 articles that included some economic assessment related to lipases (free or immobilized ones) were found, representing less than 2% of the total literature. However, further exploration revealed that most did not have an economic assessment of biocatalytic processes for ester syntheses as the real focus.

A closer look at the five most-cited articles on biocatalytic ester syntheses published since 2001 (excluding articles related to enzymatic biodiesel) revealed that all of them mentioned terms such as "costs" or "economic" and variations of those words. For example, Mohamad and co-authors (2015) [17], in their study's conclusion section, mentioned the costs of the commercial lipases Novozym 435® and Lipozyme RM IM®, indicating that the prepared biocatalyst (*Candida rugosa* lipase immobilized on carbon nanotubes) could be an advantageous alternative, but they did not include an estimation of production costs. Both the works of Gumel and co-authors (2011) [18] and Ferrer and co-authors (2005) [19] had only one mention of "cost" (or an equivalent term) in the whole text. Watanabe and co-authors (2003) [20] pointed out that esterification reactions carried out in organic solvents are costly due to the operations required for their recovery. Differently, the study of Romero et al. (2005) [21] on the enzymatic synthesis of isoamyl acetate paid more attention to economic issues, but there were no quantitative details of economic parameters in the scope of their work. Thus, the literature frequently describes the relevance of the studied esters in an industrial context and how biocatalysis can be an advantageous alternative for producing esters, including important statements about their applications on products and market size. However, the aim of these studies and the consequent discussion of the obtained results focused only on the scientific aspects of the syntheses. A recent review article about the industrial applications of enzymes published by Wu and co-authors [22] dedicated little attention to esters produced from the direct esterification of carboxylic acids and alcohols. The article mentioned the well-known case of the emollient esters produced by Evonik and the challenges related to the costs and reusability of immobilized lipases, but there was no further discussed examples of other ester syntheses at the lab-scale that scored well in terms of key performance indicators (KPIs), which indicate good potential for industrial implementation.

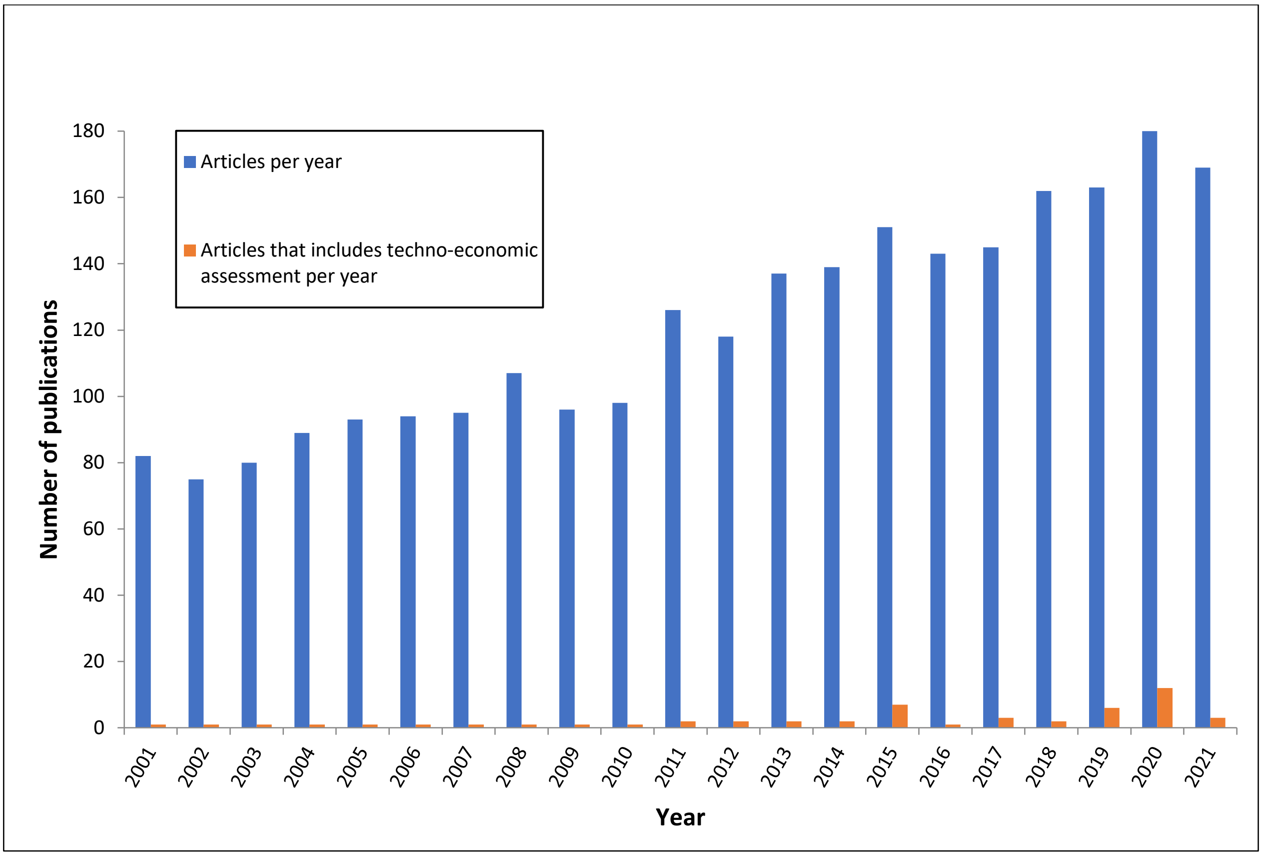

Figure 1. Evolution of scientific literature related to enzymatic ester syntheses published between 2001–2021 (blue bars) and the number of studies dedicated to the economic assessment of enzymatic ester syntheses (orange bars). Data were obtained in a survey on Web of Science database. Blue bars search strategy: ((TI = ((ester* OR "alkyl ester*" OR "flavor ester*" OR esterification) AND (lipase* OR "immobilized lipase*" OR biocataly*) AND (synthes*))) OR AB = ((ester* OR "alkyl ester*" OR "flavor ester*" OR esterification) AND (lipase* OR "immobilized lipase*" OR biocataly*) AND (synthes*))) AND DT = (Article). Orange bars search strategy: (TI = ((ester* OR "alkyl ester*" OR "flavor ester*" OR esterification) AND (lipase* OR "immobilized lipase*" OR biocataly*) AND (synthes*)) AND TS = (cost* OR econom* OR "economic assessment" OR "economic evaluation" OR "economic approach" OR "economic analysis" OR "operational costs" OR "Pilot-plant scale" OR pilot* OR feas*)) AND DT = (Article).

The technology readiness level (TRL) is a simple tool for identifying the maturity of a technology [23] that consists of a range of values that correspond to the readiness of a technology for the market (as a product or a productive process). The values (from 1 to 9) cover the proof-of-concept, lab-scale development, prototype or pilot-scale development, and commercial scale of a technology. Besides the lack of studies that evaluate the development of biocatalysis for ester syntheses using the TRL approach, we can suggest that this technology is situated between a TRL level of 4 and 5, i.e., the technology's development/validation is at the lab-scale and at the pilot-scale. Even considering that there are currently two industrial companies producing esters by biocatalytic routes, most of the scientific progress in this topic has not been validated at the pilot-scale. A preliminary economic assessment is one of the important tasks required for reaching new levels on the TRL scale. An additional tool for the development of promising scientific results into applied technologies is the elaboration of a technology roadmap, which analyzes scientific production, patents, and market aspects over time [24]. This interesting tool is widely used by companies and industries but is still less disseminated in the scientific literature for bioprocess or bioproducts, including the discussed topic here. A technology roadmap helps to identify the context of a given technology, its challenges, and its opportunities for the future. However, the limited exploration of economic aspects in the literature regarding esters obtained by biocatalysis impairs (at least in parts) the use of these useful tools in the development of biocatalytic technology for this application.

The work of Tüfvesson and co-authors (2011) [7] is an interesting case in this sense. This important article, cited 322 times until July 2022, discussed the essential aspects of the economic assessment of biocatalytic processes, including relevant quantitative data as guidelines. However, only four articles used their data or proposed methodology as an input for a new technical–economic assessment, and only one of those studies was related to biocatalysis applied for esters syntheses [25]. Thus, this analysis confirmed that, as a general tendency, in most articles of esters syntheses, the economic aspects have only received generic mentions.

2.2. The Context of Enzymatic Biodiesel and Enzymatic Specialty Ester Production

The topic "biodiesel" represents a positive exception in this field. A vast number of studies have dealt with the enzymatic process of obtaining biodiesel, and studies that discuss the economic aspects (in both quantitative and qualitative terms) of this process are more common [26–32]. Some industrial facilities around the world are currently producing enzymatic biodiesel—Aemetis Inc., Blue Sun Energy Co., Ltd., Oleofat Trader S L, Enzymocore [33–36]—and some companies in the recent past have already tried to adopt a biocatalytic route, such as Hainabaichuan Co., Ltd., (Haikou, China), Lvming Co., Ltd. (Shanghai, China), Kansai Chemical Engineering (Amagasaki, Japan), and Piedmont Biofuels (Pittsboro, CA, USA) [5,37]. Many important considerations about this field were discussed by Dutra and co-authors (2021) [5] in a detailed bibliometric analysis, including a specific topic dedicated to economic assessment. The authors discussed the opportunities and drawbacks of using inexpensive raw materials for esterification/transesterification reactions and immobilization supports of lipases. The global context of the production and consumption of biodiesel is more favorable to the adoption of enzymatic technologies, considering the market size and its dynamics, the production scale, the focus on a single product (which is different to chemical companies that work with a portfolio of products), and the regulatory issues adopted by many countries [5,37,38].

Some studies have focused on the economic aspects of the generation of enzymes with potential applications in biodiesel synthesis [39]. In these studies, to obtain a result with a comparative validity that can be reported, it is recommended that an ester synthesis productivity/enzyme cost normalization be performed. The production of enzymes for ester syntheses by submerged or solid-state fermentation and their subsequent immobilization have been widely studied; the optimization of these processes is of the utmost importance for obtaining enzymes with a high activity and stability conciliated with reasonable costs [10,40–42]. Other studies have focused on the economic analysis of the enzymatic biodiesel synthesis process [27,28], usually considering the use of commercial enzymes such as Novozym®® 435 [43]. In these cases, the enzymes are inserted in the context of an economic analysis as an extra material cost (and usually with a significant impact on the costs). In fact, enzyme-catalyzed biodiesel production processes are considerably different from conventional chemical processes, as they have the advantage of a generally simpler downstream process. On the other hand, more complex upstream operations may be necessary to avoid enzyme deactivation, such as the stepwise addition of alcohol [28].

2.3. The Relevance of Lipase Immobilization and Its Challenges

The immobilization of lipases is crucial to simplify the downstream operations in ester syntheses; however, immobilization causes a drastic increase in the costs of producing the lipases. Thus, the successful immobilization of lipases using low-cost raw materials (or even residual raw materials) is of the utmost importance for the feasibility of their use in ester syntheses [9,10,44,45]. Enzyme immobilization started as a solution for recovering and reusing very expensive biocatalysts [39,46]. At that time, the immobilization costs were compensated by the elevated price of enzymes. There are several costs related to this [43]: (i) the price of the support itself, its transport, and its storage; (ii) the immobilization process costs (including the reactor, personnel, and reagents); (iii) the costs of discarding the inactivated biocatalyst, where in many instances the support is non-biodegradable, and (iv) possible losses in enzyme activity (that can become gains if the enzyme becomes hyperactivated). However, nowadays, the prices of enzymes has gone down to levels that permit the one-cycle use of enzymes, even for the production of relatively cheap products, such as in the case of Eversa, which utilizes non-immobilized enzymes in the production of biodiesel [47]. Thus, enzyme immobilization can no longer be justified just by permitting enzyme recovery and reuse. One general advantage of having a heterogeneous biocatalyst is the easy reaction control and the possibility of utilizing many different reactor configurations [39,46]. However, proper immobilization can result in coupled immobilization and purification, saving on purification costs and time, making the immobilization step more attractive from an economic viewpoint [48].

Moreover, an adequately designed immobilization process can significantly improve many enzyme features. First, the enzyme's stability may be increased for different reasons (multipoint covalent attachment, the prevention of intermolecular processes) [49], enlarging the enzyme's operation window and improving its activity under harsh conditions (thus reducing the cost of the enzyme). Moreover, immobilization of enzyme can alter the enzyme's conformation and place the enzyme in a confined space. In a determined nanoenvironment, these can affect the enzyme's activity, selectivity, and specificity [50–53]. Thus, immobilization can become necessary to reach the desired productivity and yield in the reaction.

As esterified products currently stand, in the best case of them having a moderate price, the enzyme immobilization process should be as simple as possible. Fortunately, a straightforward immobilization protocol is especially suitable for lipases; it involves the interfacial activation of the lipases versus hydrophobic supports [54]. This protocol permits the one-step immobilization, purification, and stabilization of lipases via a reversible immobilization that can enable the reuse of the support after the inactivation of the enzyme and its release [55]. Hydrophobic supports are usually not recommended for immobilizing enzymes [56], but lipases are an exception, as the open and adsorbed lipase structure is more stable than enzymes in a conformational equilibrium [55]. Moreover, in this kind of reaction, the rapid release of hydrophilic by-products (water or glycerin) can produce a layer of this compound around the immobilized enzyme, thus driving the inhibition/inactivation of the enzyme [57–60], and this can be prevented using very hydrophobic support [58,61–64]. In any case, lipases are not soluble in organic media and may be expected to form aggregates, which will generate these problems that cannot be solved by using free enzymes.

The immobilization of enzymes, particularly lipases, is a topic that has been intensively explored in recent years. Relevant advances have been obtained regarding this issue, but a recent review article [43] highlighted some problems in the design of experiments that leads to the obtaining of sub-optimal results, indicating the need for further developments. However, as has been observed in most studies on enzymatic ester syntheses, immobilization studies, in general, do not include the quantitative economic considerations related to the immobilization processes and the raw materials involved, even when in-house preparations are compared with commercial ones [9,17,40,41,65–67].

2.4. Economic Drawbacks of Biocatalytic Ester Syntheses—Identification and Quantification of Critical Points

Bioprocesses, including biocatalytic processes and enzymatic ester syntheses, face challenging economic constraints. Generally, bioprocesses are operated under batch regimes in multipurpose/multi-product plants. Batch processes allow a remarkable flexibility in obtaining low-volume consumption products (particularly specialties or fine chemicals) among other important advantages. However, the total capital investment may be higher due to the potential need for multiple pieces of equipment as well as the variety of operational conditions and raw materials. Moreover, it is well-known that batch processes show a lower volumetric productivity, a lower equipment utilization time, less process automation, and more complex production control than continuous processes [68]. In general terms, the comparison between bioprocesses and conventional chemical processes for a specific product should be made considering at least the equivalent minimum selling prices (MSP) between both technologies and the investment payback periods between 2 and 4 years [26,69–71]. The yield, titer, and productivity are the key factors to be studied in a bioprocess (fermentation), and their correlation with economic parameters is crucial for identifying the feasibility of the process [72].

The attractiveness of scaling-up biocatalytic production could be increased using preliminary technical-economic analyses, life-cycle assessments, and technology roadmaps, elucidating the main economic drawbacks. A preliminary technical–economic analysis of a process can offer: (i) the preliminary design of the operations required for a production plant; (ii) an overview of the operational costs and capital investment for a hypothetical production plant; (iii) an overview of the minimum selling price of the product using the proposed process design and its comparison with the required investments. The intersection between the first two items is the key to identifying the critical points in terms of costs and where intense efforts in cost reduction should be applied. For example, in a previous work by our group [44], which aimed to estimate the operational and fixed costs for the production of a lipase from palm residues using solid-state fermentation, the facility-dependent operational costs had the most significant impact on the lipase cost—21.24 \$ kg^{-1}. As the facility-dependent costs were mainly composed of maintenance costs and the depreciation of the industrial unit, which in turn were directly proportional to the equipment capacity considered in the project, it was concluded that the long fermentation times needed to obtain the lipases were the real drawback in obtaining a more competitive product. This obtained result indicated the need for further studies focused on the optimization of obtaining conditions, particularly the total time of the process, the use of cheaper raw materials, and utility consumption reduction.

On the other hand, some counterintuitive observations may emerge. In a previous work [10], we identified that a biocatalyst produced by solid-state fermentation with a lower esterification activity than commercial ones (Novozym 435® and Lipozyme RM IM®) and a reduced reuse capacity in the conditions tested was more attractive than the commercial immobilized lipases due to its low production cost. Arnaldos et al. (2020) [25] observed the high relevance of the energy costs to the total costs of a lab-scale enzymatic ester synthesis due to the use of vacuum pressure to withdraw formed water. However, energy savings are usually considered to be an advantage of biocatalysis compared to conventional catalysis. Gunukula and co-authors (2017) [73], in an assessment of the biocatalytic production of different chemical building blocks, showed that MSP was much more sensitive to variations in the yield of bioprocesses than to the titer or productivity, even when considering drastic variations.

In summary, even with the wide availability of the scientific literature related to biocatalytic ester syntheses and their consistent set of potential advantages in an industrial context, there is still a gap in the literature related to techno-economic assessments on this topic. Preliminary cost analyses may open the gates to an assertive pilot plant scaling-up. Scaling-up studies on biocatalytic ester syntheses are also scarce [41,74–76]. Similar to the other cases cited here, the economics have commonly not been addressed, which limits their development towards large-scale applications.

3. Conclusions

As a direct consequence of their neglected discussion in the literature, the economic drawbacks of biocatalysis remain little known in quantitative terms. A problem cannot be solved if its dimensions are unknown. Researchers and industry executives have generic opinions about the topic; the first group usually overrates the advantages of biocatalysis, and the second one tends to classify it as costly and risky, ignoring its benefits. Measurable data (even preliminary) could be a conciliation point between academia and industry in this field. A preliminary technical–economic assessment could quickly identify the critical cost points, and bio/chemical engineering expertise can identify the proper techniques, operations, and processes designed to overcome the drawbacks. When critical points are known and quantified, answers may emerge.

Although there is no strict correlation, enzymatic biodiesel is a topic in which convergence is observed regarding the availability of techno-economic studies and commercial/pilot-plant scale production. It is symptomatic that the economic issues have been neglected in the literature related to this topic in the past two decades, with research mainly considering the relative maturity of biocatalysis applied to esters at the lab-scale. Thus, the natural next step is the application of this knowledge to a broad context, considering advances in the field related to the use of immobilized lipases. However, in-depth analyses with economic perspectives of biocatalytic routes, including life-cycle assessment studies and technology roadmaps, are urgently needed to support the relevant changes in industrial processes for ester production.

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