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Green Production of a High-Value Branched-Chain Diester: Optimization Based on Operating Conditions and Economic and Sustainability Criteria

Claudia Montiel, Silvia Gimeno-Martos, Salvadora Ortega-Requena, Mar Serrano-Arnaldos, Fuensanta Máximo and Josefa Bastida *

Chemical Engineering Department, Faculty of Chemistry, Campus of Espinardo, University of Murcia, 30100 Murcia, Spain; cmontiel@um.es (C.M.); silvia.gimeno@um.es (S.G.-M.); dortega@um.es (S.O.-R.); mar.serrano@um.es (M.S.-A.); fmaximo@um.es (F.M.)

* Correspondence: jbastida@um.es

Featured Application: In the last years, consumers' and administrations' demand for more sustainable products and processes has been increasing. This work develops a new sustainable way to obtain a branched ester for cosmetic applications (neopentylglycol dilaurate) and demonstrates that this new production route can be economically competitive.

Abstract: Branched-chain esters (BCEs) have found a large number of applications in cosmetics. Among them, neopentyl glycol dilaurate (NPGDL) stands out as an emollient, emulsifier, and skin-conditioning agent. This work presents the synthesis of NPGDL in a solvent-free medium using the two most common immobilized lipases: Novozym® 40086 (Rml) and Novozym® 435 (CalB). Results proved that the former biocatalyst has lower activity and certain temperature deactivation, although conversions $\geq$ 90% were obtained at 60 °C and 7.5% of catalyst. On the other hand, optimal reaction conditions for Novozym® 435 are 3.75% *w*/*w* of the immobilized derivative at 80 °C. Under optimal conditions, the process productivities were 0.105 and 0.169 kg NPGDL/L h, respectively. In order to select the best conditions for NPGDL production, studies on the reuse of the derivative and cost estimation have been performed. Economic study shows that biocatalytic processes can be competitive when lipases are reused for five cycles, yielding biocatalyst productivities of 56 and 122 kg NPGDL/kg biocatalyst using Novozym® 40086 and Novozym® 435, respectively. The final choice will be based on both economic and sustainability criteria. Green metric values using both biocatalysts are similar but the product obtained using Novozym® 40086 is 20% cheaper, making this alternative the best option.

Keywords: *Candida antarctica* lipase; *Rhizomucor miehei* lipase; solvent-free; neopentyl glycol dilaurate; esterification; economic assessment; green metrics

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1. Introduction

Since the last decades, societies are becoming increasingly aware of the need to achieve true economic, social, and environmental sustainability. During the 1980s, environmental actions were aimed at end-of-pipe solutions rather than at prevention measures. Now, industrial chemistry practice is focused on reducing waste generation, using safer materials, and resource efficiency, while guaranteeing high chemical yields and process economic profitability [1].

One of the greatest exponents of this change in paradigm is probably the 12 principles of green chemistry, enunciated by Anastas and Warner in 1998. Among them, the use of selective catalysis rather than stoichiometric synthetic pathways is recommended [2]. In fact, the use of catalysts is a widespread tool in the industry, and, in particular, enzyme-catalyzed processes are notably expanding. Nowadays, a great number of organic transformations

have a biocatalytic alternative [3], which may be also eco-friendlier, as has been pointed out by studies of Life Cycle Assessment [4] or green calculations [5]. In addition, the use of enzymatic biotransformations in the cosmetic sector can contribute to achieving a "natural" designation [6], which has proved to be an increasingly effective marketing claim, as consumers often perceive natural cosmetics as safer, healthier, and more respectful with the environment [7]. In this sense, many examples of the lipase-based synthesis of emollient monoesters can be found in the literature [8–11], and even some processes have successfully been implemented at an industrial scale [12].

In recent years, the interest in BCEs to obtain everyday-use products has increased due to their technical features at low temperatures [13]. In some cases, they contribute to expanding the concept of sustainability to the product itself: some BCEs are studied for obtaining greener alternatives to mineral-based lube bases due to their biodegradability [14,15]; others can be used as biodiesel additives to improve their pour and cloud point and their low-temperature filterability [16,17]. In addition, several BCEs have been described as adequate substitutes for cyclomethicones [18], whose use as a cosmetic ingredient has been banned in the European Union at concentrations above 1% from January 2020 [19]. Actually, BCEs such as NPGDL are widely used in the cosmetic industry as emollients, surfactants, and emulsifying or skin-conditioning agents [20].

In light of the above-mentioned, biocatalysis appears to be an interesting eco-friendly alternative for obtaining BCEs. In the case of the synthesis of esters from polyols, lipases from different origins have been tested with different outcomes [21–24]. For example, Aguierias et al. [21] studied the production of biolubricants from neopentyl glycol and soybean biodiesel catalyzed by two lipases from *Rhizomucor miehei* (Rml) and *Candida antarctica* (CalB), obtaining better results with the first one. On the contrary, a conversion of 98% was achieved by Gryglewickz et al. [22] using the same CalB preparation in transesterification reactions with neopentyl glycol and trimethylolpropane. In fact, these enzymes have different structural features that may be decisive for their catalytic activity under certain conditions. According to Pleiss et al. [25], the binding pocket of Rml has the shape of a bowl with a long axis that makes room for long fatty acids. On the other hand, CalB has a funnel-like binding site, which makes it more appropriate for short and medium fatty acids up to C13. Nevertheless, Naik et al. [26] describe those enzymes as completely the opposite: CalB's active site would have a large acyl binding cleft but narrow space for alcohols, while Rml may find restrictions to accommodate the acid part but not the alcohol.

As it seems unlikely to establish a priori the best lipase-based catalytic preparation, this work studies the performance of two commercial biocatalysts, Novozym® 40086 (Rml) and Novozym® 435 (CalB), in the esterification process of neopentyl glycol (NPG) and lauric acid (LA) under solvent-free conditions to produce NPGDL, a BCE used in the cosmetic industry (Figure 1).

The main objective of this present study is the proposal of a new way of manufacturing NPGDL for commercial exploitation. Therefore, it is important to include an economic study in order to select the most profitable alternative. The calculation of the process' direct costs should include energy consumption, raw materials, and the biocatalyst. As with any process using immobilized enzymes, the reuse of the enzymes must be possible to be economically attractive. This paper also explores the reusability of the immobilized derivatives Novozym® 40086 and Novozym® 435 when used for the production of NPGDL and the activity they retain after repeated cycles of use.

Biotechnological alternatives to classical processes have to demonstrate their low environmental impact in a quantitative manner. In regard to this aspect, several researchers have defined a number of sustainability indicators [27–30]. In this present paper, several of these indicators are compiled from the literature and are determined and compared for the proposed alternatives.

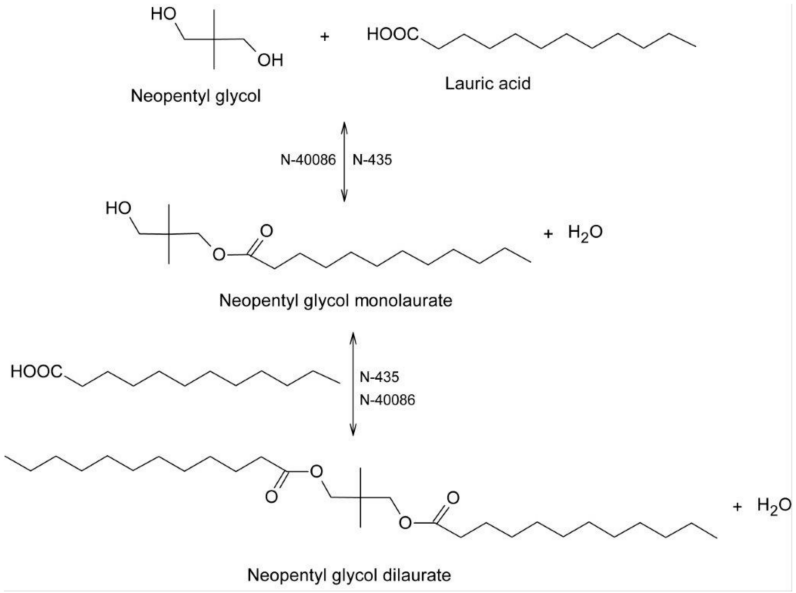


Figure 1. Scheme of the enzymatic esterification process between NPG and LA.

2. Materials and Methods

2.1. Materials

Novozym® 40086 (Rml immobilized on an acrylic carrier with a minimum activity of 250 IUN/g) and Novozym® 435 (immobilized CalB on DVB/methacrylate with a declared activity of 10,000 PLU/g) were generously donated by Novozymes, Spain S.A. Lauric acid, LA (99%), and neopentyl glycol, NPG (99%), were purchased from Acros Organics™ and Sigma-Aldrich, St. Louis, MO, USA, respectively. The rest of the reagents used were all analytical reagent grade.

2.2. Biocatalytic Synthesis

The synthesis of NPGDL was carried out in a 50 mL jacketed open-air batch reactor. All reactions were carried out in a solvent-free medium. For that purpose, 20 g of a mixture of LA and NPG in stoichiometric ratio (2:1, acid:alcohol) was placed in the reactor and allowed to melt while stirring with an IKA® RW-11 basic Lab-Egg vertical stirrer set at 350 rpm. Amounts of 0.375, 0.75, and 1.5 g (concentrations of 1.88, 3.75%, and 7.5% *w*/*w* referred to substrates) of both immobilized derivatives were tested. Temperatures ranging from 50 to 80 °C were evaluated for Novozym® 40086 but experiments with Novozym® 435 were performed using temperatures from 60 to 90 °C. In order to follow the progress of the reaction, the acid value of several samples withdrawn from the reactor during the esterification process was measured.

The acid value (AV) is defined as the milligrams of potassium hydroxide necessary to analyze the free acids contained in 1 g of sample [31]. According to this, conversion can be calculated as:

$$\text{Conversion } (\%) = \frac{AV_0 - AV_t}{AV_0} \times 100$$

where AV_0 is the acid value determined at the beginning of the reaction; and AV_t is the acid value of a sample taken at a certain time.

All experiments were performed in triplicate and the results shown in this paper are the mean value of the three measurements, including within the graphs the error bars (±standard deviation). When stoichiometric substrates ratio is used and high conversions (>95%) are achieved in a solvent-free reactor, the final product is the ester of interest and can be used without further purification.

2.3. Recovery and Reuse of the Biocatalysts

At the end of the reaction time necessary to reach maximum conversion (8 h for Novozym® 40086 and 5 h for Novozym® 435), the agitation was stopped, the immobilized enzyme was allowed to settle, and the products were removed from the reactor with the aid of a pipette. The new reaction cycle starts by adding fresh substrates to the reactor without treatment or washing of the derivative.

2.4. Energy Consumption

In order to quantify the energy costs, a clampmeter was used to measure the current intensity in real time.

First of all, it is assumed that the average voltage at the terminals of the equipment is 220 V. The energy required to heat and maintain the temperature of the reactors by means of thermostatic baths was then quantified. Initially, 10 min of continuous operation are required to reach the working temperatures (60 °C for Novozym® 40086 and 80 °C for Novozym® 435) and homogenize the reaction mixture. After that time, the thermostat switches to maintenance mode, thus reducing its energy consumption. Power requirement of mixing devices is much lower and constant over time.

2.5. Gas Chromatography Analysis (GC)

The evolution of the chemical species involved in the esterification process under optimum conditions was also followed using a 7820A gas chromatograph from Agilent Technologies, with an FID and an Agilent HP-5 silica capillary column (30 m × 0.32 mm × 0.25 μm). The temperature at the injector was 205 °C, with a split ratio of 2:1, while oven started at 80 °C (1 min) and increased to 120 °C at 75 °C min^{-1}. This temperature was held for one minute and after that, it was increased again at 20 °C min^{-1} until 300 °C, which was maintained so that the total analysis time was 20.5 min. Methyl myristate was used as internal standard (IS). As neopentyl glycol monolaurate (NPGML) is not commercially available, its concentration was calculated by difference from the total mass injected. Figure 2 shows a chromatogram where the retention times of the different compounds present in the reaction medium can be observed.

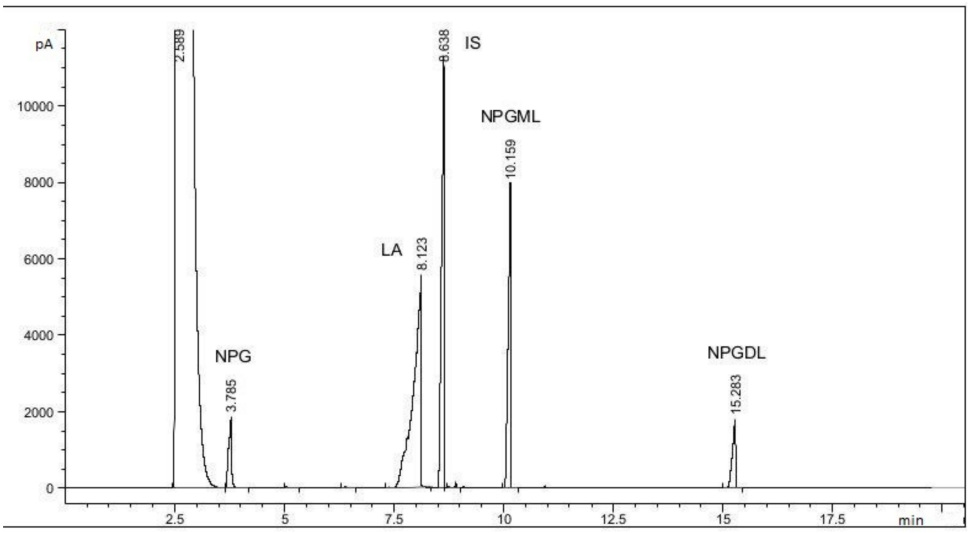


Figure 2. GC analysis of an intermediate sample of the esterification process between NPG and LA.

3. Results and Discussion

3.1. Influence of the Amount of Biocatalyst

As a general trend, increasing the amount of immobilized enzyme in the reaction medium guarantees a boost in the reaction rate. Nonetheless, this effect is usually mini-

mized at high concentrations of biocatalyst, as the number of active centers available may exceed the needs of the process and, therefore, lead to unnecessary expenses [32,33].

Figure 3 shows the influence of the concentration of Novozym® 40086 (a) and Novozym® 435 (b) at 70 °C, showing that in both systems, the reaction rate is significantly improved when increasing the amount of biocatalyst within the range studied. In this sense, doubling the concentration of Novozym® 40086 from 1.88% to 3.75% (*w*/*w*) has an important effect on the process: only a conversion of ~20% is achieved after 24 h with the lowest quantity tested, while such value is attained after 6 h by using a 3.75% (*w*/*w*) of immobilized derivative. However, the best results are obtained with a concentration of 7.5% (*w*/*w*), with a final conversion of 91.2% being chosen as optimum. On the other hand, in Figure 3b it can be noticed that, even if increasing the amount of Novozym® 435 implies less reaction time to achieve a certain yield, a conversion of ~90% is obtained with just one hour of difference when using 3.75 or 7.5%, therefore 3.75% has been selected. These results are similar to the ones reported by other authors during the esterification process of NPG with free fatty acids with 4% of commercial immobilized lipases at 40 °C [21].

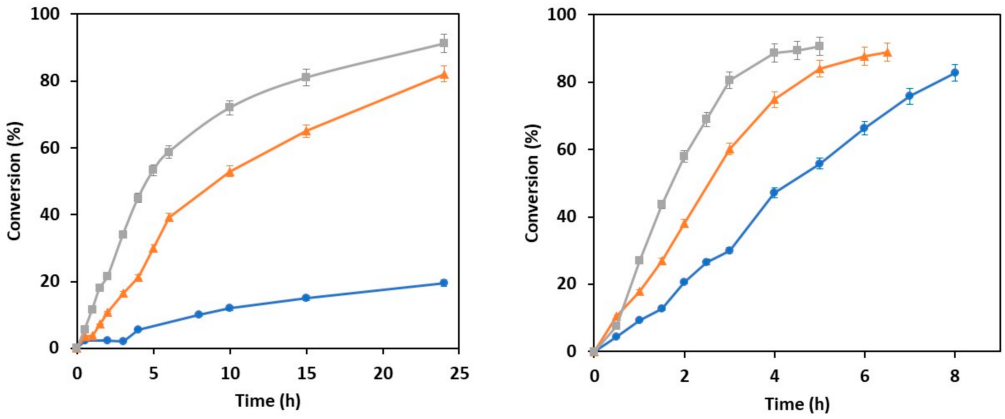


Figure 3. Influence of Novozym® 40086 (**a**) and Novozym® 435 (**b**) concentration in the solvent-free synthesis of NPGDL at 70 °C: ● 1.88%, ▲ 3.75%, and ■ 7.5%.

From the previous discussion, it is also obvious that Novozym® 40086 shows a lower activity than Novozym® 435, and this difference might be attributed to factors inherent to the enzymes themselves, either their substrate preferences or their resistance to temperature under reaction conditions (or a combination of them).

According to the work of Pleis et al. [25], both enzymes are able to accept acyl donors of 12 carbon atoms. Consequently, the low activity of Novozym 40086 cannot be attributed to the acid. What is more, by reviewing the literature, several examples can be found proving the good performance of Rml and CalB biocatalysts in esterification processes with longer acids [33–36]. Thus, regarding substrate specificity, it seems that the main difference in their activity could lie in their affinity for NPG.

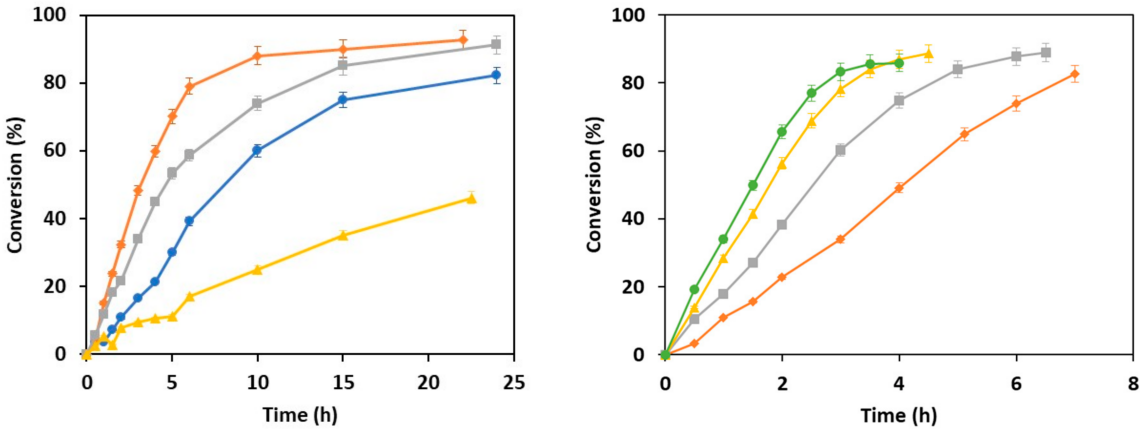
On the other hand, previous work from the authors has pointed out the great performance of Novozym® 435 and both Novozymes' Rml biocatalysts, Lipozyme® RM IM and Novozym® 40086, during the solvent-free synthesis of monoesters at temperatures over 70 °C [33,36,37]. Nevertheless, in view of the results depicted in Figure 3, a negative effect of reaction temperature on Novozym® 40086 cannot be discarded, and the effect of this variable will be discussed in the subsequent section.

3.2. Influence of the Temperature

The optimization of the process temperature is of great importance in enzymatic reactions. Concretely, in large-scale solvent-free systems, three main aspects must be considered when increasing temperature [37,38]:

1. It may cause enzyme denaturation;
2. If not, it usually involves an improvement in reaction rate and a lower reaction media viscosity;
3. Even if a biocatalyst's activity is incremented by temperature, the process energy consumption may not be cost-effective.

The influence of the temperature in the synthesis of NPGDL with 7.5% (*w*/*w*) of Novozym® 40086 and 3.75% (*w*/*w*) of Novozym® 435 is represented in Figures 4a and 4b, respectively.



(**a**) (**b**)

Figure 4. Influence of temperature on solvent-free synthesis of NPGDL with Novozym® 40086 (**a**): ● 50 °C, ♦ 60 °C, ■ 70 °C and ▲ 80 °C; and Novozym® 435 (**b**): ♦ 60 °C, ■ 70 °C, ▲ 80 °C and ● 90 °C.

According to the manufacturer, the optimum temperature range for working with Novozym® 40086 is from 30 to 50 °C [39] but considering the author's previous experience, temperatures from 50 to 80 °C were tried. As can be seen in Figure 4a, decreasing the temperature from 70 °C to 60 °C led to higher yields in shorter reaction times, and after 6 h the conversion was ~80%, about 20 units more than the one obtained at 70 °C (although values $\geq$ 90% where reached in both systems after 24 h). The negative effect of raising temperatures above 60 °C is confirmed when operating at 80 °C, as the reaction rate is dramatically reduced, and by the end of the assay, only a 46.1% of conversion was attained. On the other side, when the temperature is lowered to 50 °C, the reaction rate is not only slower than at 60 °C but also than at 70 °C, which suggests that the viscosity of the reaction medium should have been increased and so, mass transfer limitations should have been enhanced.

On what concerns Novozym® 435, from Figure 4b it can be concluded that increasing the temperature has a positive impact on esterification. In fact, Novozymes affirms that this commercial lipase may work from 20 to 110 °C and different studies confirm its effectiveness at high temperatures, whether working with organic medium or in solvent-free systems [39–41]. This effect is less pronounced for the highest temperatures tested: for example, after 3 h of reaction, conversion is 1.8 times higher at 70 °C than at 60 °C but it is only increased by 1.3- and 1.1-fold when raising temperatures to 80 and 90 °C, respectively. Considering that conversion of ~90% is attained in 6.5 h at 70 °C, but two hours before if the temperature is increased by 10 °C, 80 °C was selected as the optimum for operating with Novozym® 435.

3.3. Biocatalyst Comparisons under Best Reaction Conditions

The results previously discussed have made patent the differences between the performances of the biocatalysts under the same reaction conditions. Even though, when

optimized values are used, the lower temperature required by Novozym® 40086 and its lower cost may compensate for the fact that Novozym® 435 seems more effective from a technical point of view [32].

Figure 5 compares the reaction course under the best reaction conditions for Novozym® 40086 (7.5% *w*/*w* and 60 °C) and Novozym® 435 (3.75% *w*/*w* and 80 °C), where it can be observed that Novozym® 435 leads to a conversion of 90.03% after 5 h, while the 242 value for Novozym® 40086 is 72.28% at the same time. A similar final conversion (91.03%) will not be attained by Novozym® 40086 until three hours later, which may be excessively longer to compensate for the savings of operating 20 °C below than with Novozym® 435.

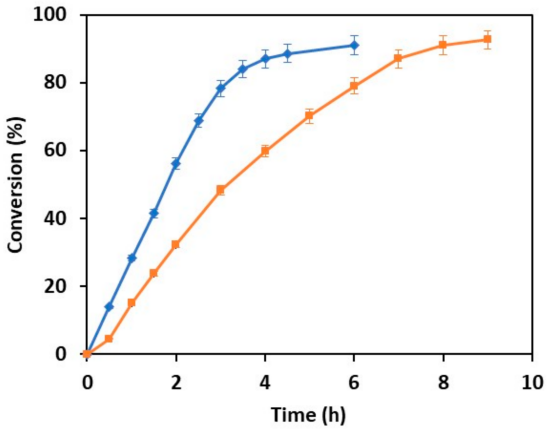


Figure 5. Comparison of NPGDL synthesis under best reaction conditions: ■ Novozym® 40086 (7.5%, 60 °C) and ♦ Novozym® 435 (3.75%, 80 °C).

Under these conditions, the calculated NPGDL productivities are 0.105 kg/L h for the case of using Novozym® 40086 and 0.169 kg/L h if the lipase is Novozym® 435. These productivities are similar to those declared in other studies of ester production in solvent-free systems. Thus, some authors reported productivities of 0.033 kg/L h in the production of panthenyl triacetate [42], 0.15 kg/L h for neopentyl glycol dicaprilate/dicaprate [43], and a value of 0.217 kg/L h panthenyl monolaurate [44].

In order to monitor the evolution of all the chemical species involved (substrates, intermediates, and final products) under the best reaction conditions, the GC analysis of the samples withdrawn over time was performed. The results are shown in Figure 6, from which it can be confirmed that high yields were achieved with Novozym® 40086 (a) and Novozym® 435 (b) during the esterification process. As NPGML is an intermediate product of the reaction, its concentration increases over time, reaching a maximum value after ~1.5 h of reaction for both biocatalysts and then decreasing as the esterification of the remaining hydroxyl group occurs. By observing the NPGDL curve, it can be noticed that the final product is obtained since the beginning of the reaction and that the esterification of the first hydroxyl group happens faster than the second, as, logically, the diester formation depends on the amount on intermediate available. In addition, by comparing Figure 6, it can be noticed that the reaction rate of these secondary steps is higher with Novozym® 435 than with Novozym® 40086, which explains why the former reaction system requires less reaction time. Regardless of that, when both reactions are allowed to evolve, final products are composed mainly of NPGDL with a small amount of LA unreacted, even though both substrates are initially provided in stoichiometric amounts. This is probably due to the evaporation of NPG [45], as, in fact, no traces of the alcohol or the intermediate product (NPGML) were found in the final product samples. In both cases, high yields and products of purity above 95% are obtained, comparable with many cosmetic ingredients.

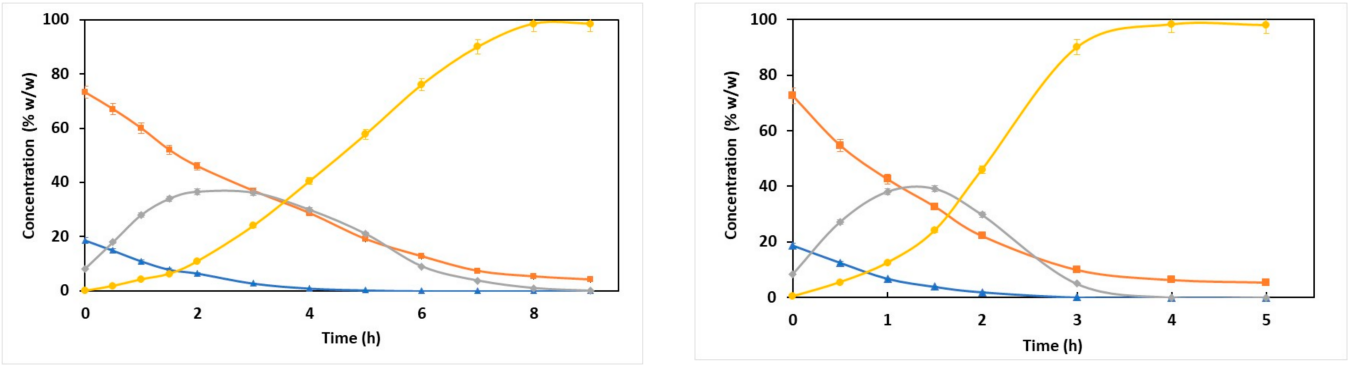


Figure 6. Evolution of NPGDL synthesis under best reaction conditions with Novozym® 40086 (**a**) and Novozym® 435 (**b**): ■ LA, ▲ NPG, ♦ NPGML, and ● NPGDL.

While considering that temperature plays a decisive role in Rml biocatalyst activity, the results obtained once this parameter has been optimized suggest that an enzyme's preference for certain substrates is still a factor to consider in evaluating their performance. As stated in Section 3.1, from the available literature it can be concluded that both enzymes are not affected by an LA carbon chain length, so, in view of the foregoing, CalB activity appears to be more specific to the branched polyol NPG than Rml's, or even to the monoester formed after the first step of the process, the NPGML. Although great differences can be established between reaction systems, the present results appear to disagree with the classification made by Naik et al. [26] when studying the lipase-based hydrolysis of several esters, where Rml was described as an enzyme with a large alcohol-binding cleft and an acyl narrow one, while CalB would be just the opposite.

3.4. Biocatalyst Selection Based on Economic Evaluations and Sustainability Indicators

It is widely described that, for a biocatalytic process to be economically viable, it is essential that the biocatalyst can be reusable in consecutive reaction cycles, as it is the factor that most influences the final cost of the process [43]. In this present work, the synthesis of NPGDL has been performed in five successive batches reusing both immobilized lipases (Novozym® 40086 and Novozym® 435) under study. For this purpose, the procedure described in Section 2.3 has been applied and the results obtained are shown in Figure 7. As can be seen, both biocatalysts preserve a high percentage of their initial activity (84.5% Novozym® 40086 and 99.2% Novozym® 435) after five successive uses. These figures again highlight the poorer behavior of Rml lipase, as already discussed in previous sections.

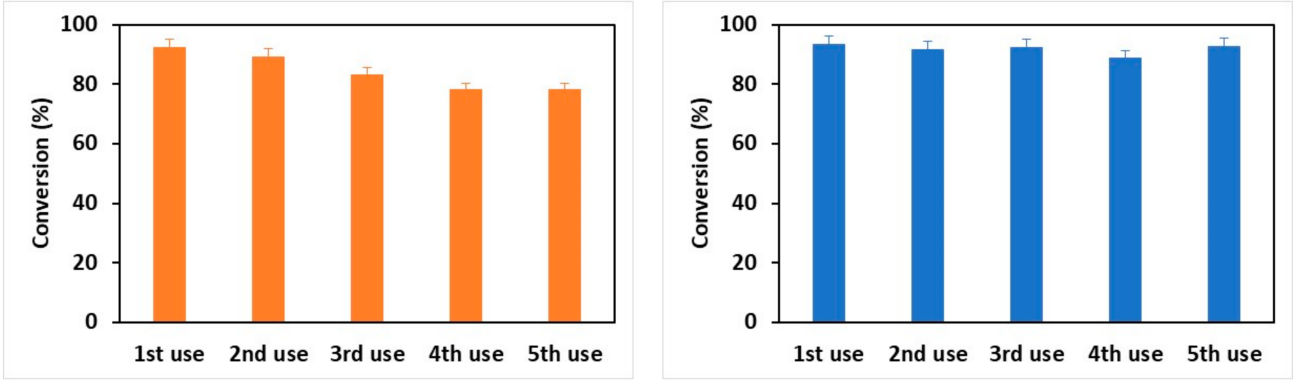


Figure 7. Reuse of biocatalysts Novozym® 40086 (**a**) and Novozym® 435 (**b**) under the best operational conditions: (**a**) 7.5% *w*/*w*, 60 °C, 8 h; (**b**) 3.75% *w*/*w*, 80 °C, 5 h.

The biocatalyst productivity of the process using both lipases increases significantly with the reuse of lipase. Thus, for the immobilized derivative Novozym® 40086, it increases from 12 kg NPGDL/kg biocatalyst with single-use to 56 kg NPGDL/kg biocatalyst when used five times. A similar increase is observed for the case of Novozym® 435 (from 25 kg NPGDL/kg biocatalyst for one use to 122 kg NPGDL/kg biocatalyst for five uses). In this scenario, the productivity values were approximately double when Novozyme® 40086 was used since, as mentioned above, the optimal enzyme concentration to achieve similar conversions is half when Novozym® 435 is used.

The development of a preliminary economic study is an indispensable tool that allows the final choice of the biocatalyst to be used in the synthesis of NPGDL, as well as establishing the possibility of a future industrial implementation of this process. Therefore, in this paper, this study has been undertaken on the following basis:

1. Direct operating costs have been calculated for the production of 1 kg of NPGDL;
2. Unit prices for both substrates have been obtained from suppliers who provide them in bulk, with a minimum purchase of 1 kg;
3. The immobilized lipases have been donated by Novozymes, España S.A., and their prices were specified in personal communication;
4. The energy costs have been calculated by measuring the energy consumption of the thermostatic bath and overhead mixer (Section 2.4) and considering an energy price of 0.2288 EUR/kW h (the average value of the second half-year of 2022 in Spain);
5. Five consecutive uses of the biocatalysts have been considered in the calculations.

Table 1 shows the costs of each item and, in the last row, the total direct production costs for each process.

Table 1. Substrates, biocatalysts, and energy prices. NPGDL total direct production costs using Novozym® 40086 and Novozym® 435.

	Cost	Cost (EUR/kg NPGDL)	
		Novozym® 40086	**Novozym® 435**
Lauric acid [1]	2 EUR/kg	1.41	1.30
Neopentyl glycol [2]	1.5 EUR/kg	0.49	0.45
Biocatalyst [3]			
Novozym® 40086	600 EUR/kg	10.69	
Novozym® 435	1300 EUR/kg		10.64
Thermostatic bath			
Initial	$6.8\ 10^{-3}$ EUR/min	3.23 (8 min)	5.19 (14 min)
Maintenance	$2\ 10^{-4}$ EUR/min	6.27 (8 h)	13.10 (5 h)
Overhead stirrer	10^{-4} EUR/min	3.18	1.71
Total direct cost		25.28	32.39

[1] https://hbzy-566.en.made-in-china.com/product-group/DbhnOjyGbpUa/Lauric-Acid-catalog-1.html (accessed on 17 May 2023). [2] https://lookchemical.en.made-in-china.com/product/keywordSearch?searchKeyword=neopentyl+glycol&viewType=1 (accessed on 17 May 2023). [3] Gift. Personal communication.

As can be seen, the production of NPGDL using Novozym® 40086 is the most cost-effective process due to its lower price and the fact that the synthesis takes place at a moderate temperature although it requires relatively high operating times. It is important to note, that in a future industrial application of the biocatalytic process, the energy costs would be lower than those shown in Table 1 since the energy consumption of laboratory equipment connected to a domestic electrical network has been considered and the prices do not correspond to those of the industrial market. It has been described that the energy cost of a medium-sized industry can be as much as half that of a residential system [37].

Finally, to establish whether the biocatalytic synthesis of the cosmetic ingredient NPGDL meets the criteria of green chemistry, some of the most commonly used sustainability indicators have been calculated and the results obtained are shown in Table 2.

Table 2. Green metrics for the biocatalytic synthesis of NPGDL using Novozym® 40086 (7.5% *w*/*w*, 60 °C) and Novozym® 435 (3.75% *w*/*w*, 80 °C).

	Novozym® 40086	**Novozym® 435**
Atom economy (AE) [1] (%)	92.87	92.87
Simple E-factor [2]	0.017	0.018
Complete E-factor [3]	0.095	0.093
Carbon mass efficiency (CME) [4] (%)	91.35	91.46
Process mass intensity (PMI) [5]	1.05	1.15

[1] $\mathrm{AE} = \frac{\text{molecular weight of desired product}}{\Sigma\text{molecular weight of all substrates}} \times 100$. [2] $\mathrm{E-factor} = \frac{\text{kg of waste}}{\text{kg of desired product}}$. [3] $\mathrm{Complete\ E-factor} = \frac{\text{kg of waste (including water)}}{\text{kg of desired product}}$. [4] $\mathrm{CME} = \frac{\text{kg of carbonated desired product}}{\text{kg of carbonated reactants}} \times 100$. [5] $\mathrm{PMI} = \frac{\text{kg of all materials}}{\text{kg of desired product}}$.

For both immobilized lipases, the same value of Atom Economy (AE) is obtained since its calculation is based on the stoichiometry of the reaction and is higher than 90%, which shows the sustainability of the process [27]. The Environmental Factor (E-factor) quantifies the amount of waste produced in a process and, obviously, its value must be close to zero. The specialized literature suggests calculating two types of E-factor: the simple E-factor and the complete E-factor, which includes water as a residue [28,29]. The very low values obtained for both E-factors indicate that the process studied produces a minimum quantity of residues, the main one being the water formed in the esterification reaction. Both values are significantly lower than those described for bulk chemical synthesis processes [28]. Finally, the sustainability of the processes is also evidenced by the Carbon Mass Efficiency (CME) [30] and Process Mass Intensity (PMI) [29] values, which, in both cases, present values above 90% and close to unity, respectively.

In view of the above, it can be affirmed that, from the sustainability point of view, the use of either of the two biocatalysts tested in this paper is suitable to carry out the NPGDL synthesis reaction in accordance with the main green metrics and, therefore, the final choice of the biocatalyst is not conditioned by these indicators.

4. Conclusions

In this study, the performance of two commercial lipase-based biocatalysts, the novel Novozym® 40086 and the well-known Novozym® 435, has been evaluated in the solvent-free synthesis of NPGDL, a common skin-conditioning and emulsifying agent. For this purpose, the enzyme concentration and temperature have been optimized, proving the great impact of this latter parameter in the performance of *Rhizomucor miehei* lipase, since a decrease in its catalytic activity has been observed when operating above 60 °C. Results under the best reaction conditions have proven the great performance of Novozym® 435, which is not only more thermostable but also appears to have a higher specificity for the substrates and the intermediate product involved in this solvent-free esterification process.

However, when further progress is made in the comparative study of both biocatalysts, with the aim of establishing the most advantageous industrial process for the production of neopentyl glycol dilaurate, the best choice is a different one. Once the conditions in which both enzymatic derivatives can be reused have been established, and the direct production costs of the NPGDL have been calculated, Novozym® 40086 becomes the most cost-effective alternative. The direct costs, i.e., the sum of raw materials, biocatalyst, and energy consumption, is 25.28 EUR/kg if the enzyme used is Novozym® 40086, and 32.39 EUR/kg if Novozym® 435 is chosen.

From a sustainability point of view, these processes that use enzymes as catalysts do not use any solvents in the reactor, and achieve high conversions that are environmentally friendly. The calculated sustainability indicators are evidence of this statement. In any case, the choice of one or the other would also be in favor of Novozym® 40086, which has a lower optimum working temperature.

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