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Green Synthesis of Ultraviolet Absorber 2-Ethylhexyl Salicylate: Experimental Design and Artificial Neural Network Modeling

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Abstract: 2-Ethylhexyl salicylate, an ultraviolet filter, is widely used to protect skin against sunlight-induced harmful effects in the cosmetic industry. In this study, the green synthesis of 2-ethylhexyl salicylate using immobilized lipase through a solvent-free and reduced pressure evaporation system was investigated. A Box–Behnken design was employed to develop an artificial neural network (ANN) model. The parameters for an optimal architecture of an ANN were set out: a quick propagation algorithm, a hyperbolic tangent transfer function, 10,000 iterations, and six nodes within the hidden layer. The best-fitting performance of the ANN was determined by the coefficient of determination and the root-mean-square error between the correlation of predicted and experimental data, indicating that the ANN displayed excellent data-fitting properties. Finally, the experimental conditions of synthesis were well established with the optimal parameters to obtain a high conversion of 2-ethylhexyl salicylate. In conclusion, this study efficiently replaces the traditional solvents with a green process for the synthesis of 2-ethylhexyl salicylate to avoid environmental contamination, and this process is well-modeled by a methodological ANN for optimization, which might be a benefit for industrial production.

Keywords: 2-ethylhexyl salicylate; ultraviolet filters; lipase; Box–Behnken design; artificial neural network

1. Introduction

With expanding public awareness of the photoprotection against photoaging and the carcinogenic potential of UV radiation, the sunscreen filters in the cosmetic industry is growing in demand. 2-Ethylhexyl salicylate, a well-known ultraviolet (UV) absorber, is widely used in cosmetic/sunscreen compositions suited for enhanced photoprotection of human skin and/or hair against the harmful effects of UVA and UVB irradiation [1]. It can promote an intramolecular excited-state proton transfer and facilitate the non-radiative dissipation of the absorbed UV energy, leading to a high photostability [2]. Although 2-ethylhexyl salicylate is the most widely used UV absorber in the cosmetic industry, few reports have been found in the literature about the synthesis of salicylate esters [3,4]. Chemical synthesis of 2-ethylhexyl salicylate requires high reaction temperatures (>150 °C), high pressure, long reaction times, and a catalyst (tin, titanium, ferric chloride, or sulfuric acid). The high temperatures and long reaction times lead to the degradation of reactants, and it also has a high energy cost.

In general, lipase is an essential enzyme that can catalyze the hydrolysis of lipids in order to digest and transport dietary lipids in living organisms. However, the immobilized lipases, such as Novozym®435, have been used commonly in organic chemistry synthesis, including hydrolysis and various types of esterification reactions [5]. In recent years, using immobilized lipase to catalyze specific reactions for the production of valuable molecules, such as nutraceutical and pharmaceutical compounds, has been widely developed [6–8]. Compared to chemical methods, ester synthesis using immobilized lipase shows several advantages, including higher yields and purity of products without long-term reaction times and high temperatures, and lower energy consumption. Immobilized lipases from *Candida antarctica* (CALB) are efficient and selective as biocatalysts, possessing enzymatic characteristics of both a great reactivity and a stability for esterification and transesterification reactions, and have been widely applied in the production of biodiesel [9], phytochemicals [10], sugar ester [11–13], vitamin esters [14,15], and aromatic compounds [16]. However, there have been no reports regarding the lipase-catalyzed synthesis of 2-ethylhexyl salicylate. In this study, a reduced pressure evaporation system combined with a solvent-free system for the lipase-catalyzed synthesis of 2-ethylhexyl salicylate was developed. Lipase-catalyzed ester synthesis under reduced pressure has a long history. Even in the 1990s, the reaction conditions had already been established towards the production of useful compounds [17,18]. Based on the global impact of the principles of green chemistry and sustainability, the E factor, defined as the mass ratio of waste to the desired product, has been developed for measuring the environmental acceptability of chemical processes. The role of green chemistry in waste minimization is an important issue in chemical industries [19,20]. The solvent-free system is a simple mixture of substrates, offering a maximization of substrate concentration, greater volumetric production, and cost savings in product separation [21,22]. In addition, the by-product generated in the reaction can be removed using a reduced pressure evaporation system to increase the conversion of 2-ethylhexyl salicylate.

The design of the experiments in various studies consists in a set of techniques that are expected to investigate the parameter effects on targeted response. Response surface methodology (RSM), one of the mathematical and statistical methods, is well established for designing, predicting and building experimental models, evaluates the relative significance of independent parameters, and is able to investigate the optimal conditions and responses [23,24]. Recently, compared to RSM, artificial neural network (ANN) technology has been well developed for modeling experimental/industrial processes to be a better alternative in terms of understanding process optimization. In fact, the nonlinear relationship between dependent/independent variables can be easily displayed via ANN operation without any preliminary correlation of targeted responses [25,26], indicating that ANN could be a powerful tool to request higher accuracy and efficiency for the flexible fitting of experimental responses, prediction, and modeling of industrial processes [27].

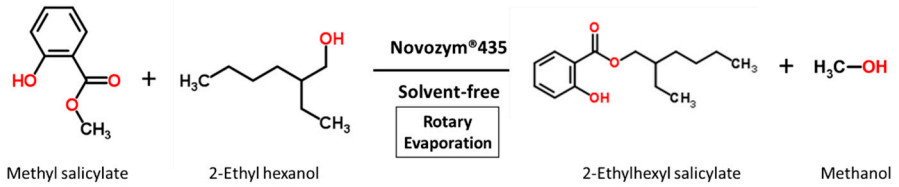
This study aimed to develop an eco-friendly process using immobilized lipase (Novozym®435) as a catalyst for the synthesis of 2-ethylhexyl salicylate in a solvent-free and reduced pressure evaporation system. ANN was employed to investigate the effects of reaction variables (reaction time, reaction temperature, and enzyme amount) on the response (conversion %) and to obtain optimal conditions. The lipase-catalyzed process might provide an eco-friendly approach to producing 2-ethylhexyl salicylate for the cosmetic industry.

2. Results and Discussion

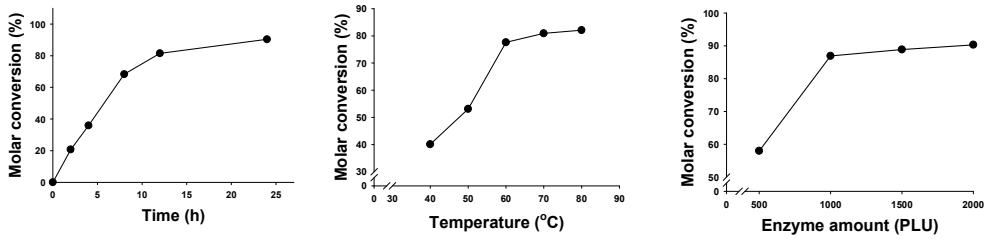
2.1. Preliminary Test

In this study, the solvent-free and reduced pressure evaporation systems were conducted for the lipase-catalyzed synthesis of 2-ethylhexyl salicylate from methyl salicylate and 2-ethyl hexanol. The scheme of the transesterification of methyl salicylate catalyzed by lipase is represented in Scheme 1. The effect of reaction time on the lipase-catalyzed synthesis of 2-ethylhexyl salicylate under the experimental conditions of reaction temperature of 70 °C and an enzyme amount of 1000 PLU

(propyl laurate unit) is shown in Figure 1A. The molar conversion of 2-ethylhexyl salicylate increased to 80% at 12.5 h. In such conditions, the molar conversion of 2-ethylhexyl salicylate was nearly constant when the reaction time was over 16 h. The effect of reaction temperature on the lipase-catalyzed synthesis of 2-ethylhexyl salicylate under a reaction time of 16 h and an enzyme amount of 1000 PLU is shown in Figure 1B. According to this result, the molar conversion of 2-ethylhexyl salicylate increased to ~80% at 60 °C. Previous papers reported that temperatures above 50 °C might possibly result in lipase inactivation, which might attenuate the increased reaction rate in response to the elevated temperature [28,29]. However, the molar conversion was increased in response to elevated temperature in the range of 50–70 °C, suggesting that the reduced pressure evaporation system might attenuate the decrease in lipase activity. Figure 1C indicates the effect of enzyme amount on the lipase-catalyzed synthesis of 2-ethylhexyl salicylate under a reaction time of 16 h and a reaction temperature of 70 °C. The result show that the molar conversion of 2-ethylhexyl salicylate was positively related to the added enzyme amount, and the molar conversion reached the highest levels when the enzyme amount was over 1000 PLU. To model the lipase-catalyzed 2-ethylhexyl salicylate synthesis, the reaction temperature (50–70 °C), the enzyme amount (500–1000 PLU), and the reaction time (8–24 h) were employed in a 3-level-3-factor Box–Behnken design (BBD). On the basis of BBD data, the optimal reaction conditions for 2-ethylhexyl salicylate synthesis were further established by the ANN.



Scheme 1. Enzymatic synthesis of 2-ethylhexyl salicylate under solvent-free and vacuum system.



(**A**) (**B**) (**C**)

Figure 1. Effects of experimental parameters on the molar conversion of 2-ethylhexyl salicylate. (**A**–**C**) Effects of (**A**) reaction time, (**B**) temperature, and (**C**) enzyme amount on molar conversion of 2-ethylhexyl salicylate.

2.2. Artificial Neural Network

ANN is a system with the ability to predict a set of input variables into a set of outcomes [30], which has been successfully applied to investigate the possible interactions of reaction parameters and to optimize various valuable ester synthesis by lipase [31]. The present study used ANN for performing the experimental design of 2-ethylhexyl salicylate synthesis in a solvent-free system. The independent parameters selected for the experimental design, namely, reaction temperature, reaction time, and enzyme amount, and their ranges, as well as levels, are listed in Table 1. In this study, the data generated from BBD design (Table 1) were used in ANN for modeling the enzymatic synthesis of 2-ethylhexyl salicylate. The architecture of the ANN model was developed by the proposed ANN consisted of three layers in the present work: (a) an input layer with three neurons (reaction time,

reaction temperature, and enzyme amount); (b) a hidden layer with several neurons; (c) an output layer containing one output neuron (molar conversion). The transfer function (Figure 2A,B), the iteration (Figure 2C,D), and the learning algorithm (Figure 2E,F) of the proposed ANN were also determined statistically according to the coefficient of determination (R^2) and root-mean-square error (RMSE) values. According to Figure 2, the best network performance could be achieved in the hidden layer of ANN with 6 neurons, which exhibited the lowest and most stable RMSE levels and the highest and most stable R^2 levels. Therefore, a 3-6-1 topology of the ANN was established (Figure 3). Based on the maximization of the R^2 value and the minimization of the RMSE value from the factorial tests, the best ANN model with a 3-6-1 topology in this study was finally determined to be a multilayer feed forward connection trained by the quick propagation (QP) algorithm, all the data were normalized using a hyperbolic tangent (Tanh) transfer function, and the iteration was performed for 10,000 to avoid overtraining and to decrease training time in this model. The learning was acquired with RMSE = 2.072 and R^2 = 0.988, respectively (Figure 4).

According to Figure 5A, the reaction temperature exhibited a great effect on the conversion with a relative importance of approximate 65%. These results are consistent with the response surface plots shown in Figure 5B. In order to validate and test the extrapolative capability of the ANN model, a completely new set of five experiments was also conducted on the experimental range that did not belong to the design data sets. The experimental and predicted values of responses by ANN modeling are given in Table 2. The performance of the newly constructed ANN model was statistically measured based on R^2 and RMSE values. The RMSE and R^2 for ANN were 2.072 and 0.988, respectively. From the results, it could be observed that the predictive ability of the ANN was found to be strong in prediction. A previous report also suggests that ANN displays a great data-predicting ability in the lipase-catalyzed synthesis of palm-based wax ester [32]. The result shows that the R^2 value calculated between the actual and ANN-predicting responses was close to 1, which also indicates that the ANN methodology can be a very powerful and flexible tool for modeling the process of enzyme-mediated synthesis. Finally, the optimal conditions for the lipase-catalyzed synthesis of 2-ethylhexyl salicylate determined by the Neural Power software were a reaction time of 23.1 h, a reaction temperature of 66.5 °C, and an enzyme amount of 881 PLU, and an optimal conversion of 88.2% could be obtained. It has been reported that the synthesis of 2-ethylhexyl-p-methoxycinnamate by immobilized lipase at a temperature of 45 °C and an enzyme amount of 750 U resulted in a yield of 91.3% in 96 h [33]. In other literature, we found that enzyme activity might be inhibited by hydrophilic alcohols such as ethanol [34]. However, in our present and in previous studies [35], the hydrophobic alcohols were commonly used as organic solvents to help lipase-mediated biosynthesis without markedly negative effects on enzymatic activity, even under the overdose treatment of solvent (the molar ratios of alcohol were 71.94 and 64, respectively). As compared to our result from the ANN analysis, the solvent-free and reduced pressure evaporation system, with a suitable reaction temperature and time, may be an excellent strategy to obtain a higher molar conversion yield of 2-ethylhexyl salicylate and an easier recovery of the final product.

Table 1. The proposed Box–Benhken design (BBD) and experimental data.

Temperature (°C)	Time (h)	Enzyme Amount (PLU)	Molar Conversion (%) [a]
50	16	500	26.1 ± 3.2
60	16	750	66.7 ± 4.7
60	24	500	62.6 ± 2.8
70	24	750	88.4 ± 1.5
60	16	750	65.5 ± 6.4
50	16	1000	53.1 ± 3.1
70	16	500	58.0 ± 2.8
50	8	750	23.3 ± 4.3
60	16	750	74.5 ± 1.5
70	16	1000	80.9 ± 4.2
70	8	750	61.6 ± 2.7
60	24	1000	86.9 ± 1.9
50	24	750	54.6 ± 0.8
60	8	500	36.1 ± 2.6
60	8	1000	56.4 ± 3.5

[a] Data are expressed as mean ± SD (n = 3).

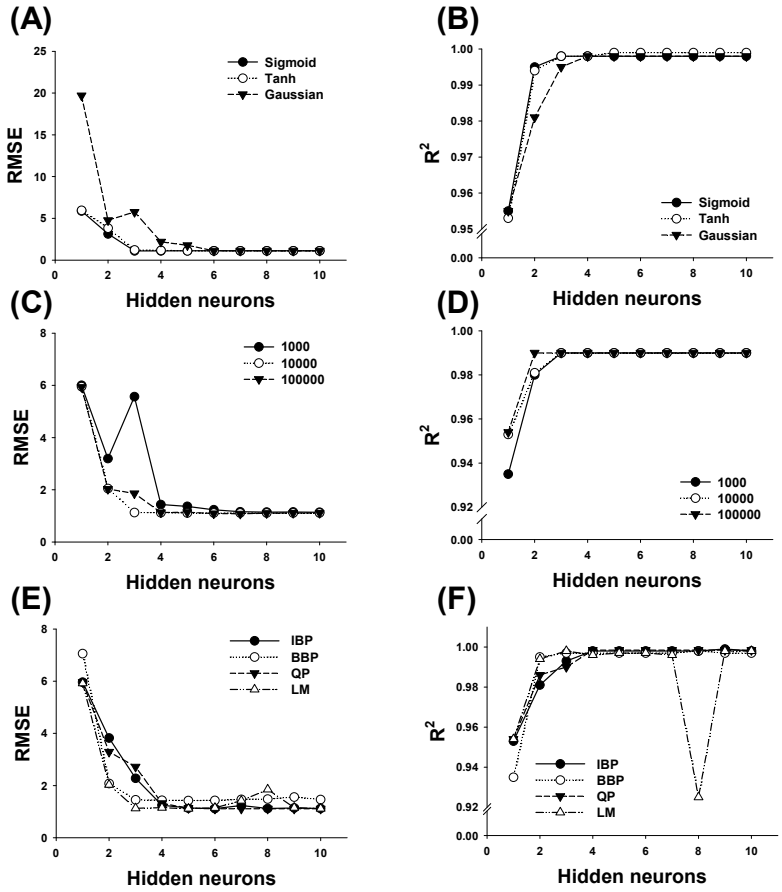


Figure 2. Effects of the transfer function, iteration, learning algorithm and number of hidden neurons on the performance of the artificial neural network (ANN). (**A**,**B**) Effects of sigmoid, hyperbolic tangent (Tanh), and Gaussian transfer functions employed in the training sets on the performance of ANN. (**C**,**D**) Effects of iteration (1000–100,000) on the performance of ANN. (**E**,**F**) Effect of learning algorithm and number of hidden neurons on the performance of ANN. IBP: increment back propagation; BBP: batch back propagation; QP: quick propagation; LM: Levenberg–Marquardt algorithm. ANN performance was evaluated by coefficient of determination (R^2) and root-mean-square error (RMSE).

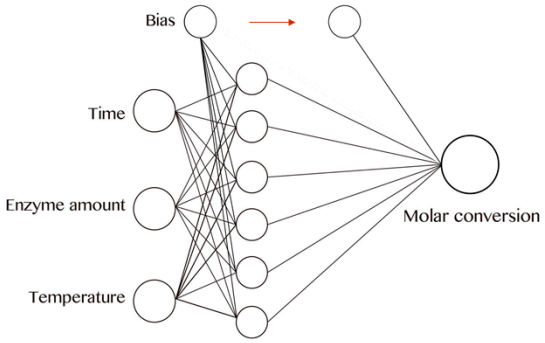


Figure 3. The illustration of multilayer feed-forward neural network. The neural network having three inputs of variables (reaction temperature, reaction time, and enzyme amount), one hidden layer with six neurons (nodes) and one output of response (molar conversion of 2-ethylhexyl salicylate).

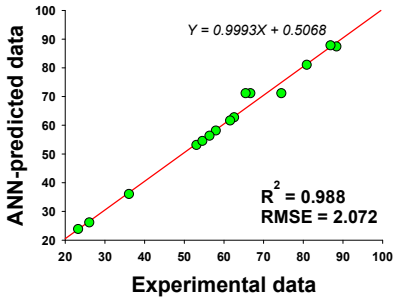


Figure 4. The performance of constructed ANN on data fitting. ANN performance was evaluated by a coefficient of determination (R^2) and a root-mean-square error (RMSE). Residual values: ANN-predicted values minus experimental values.

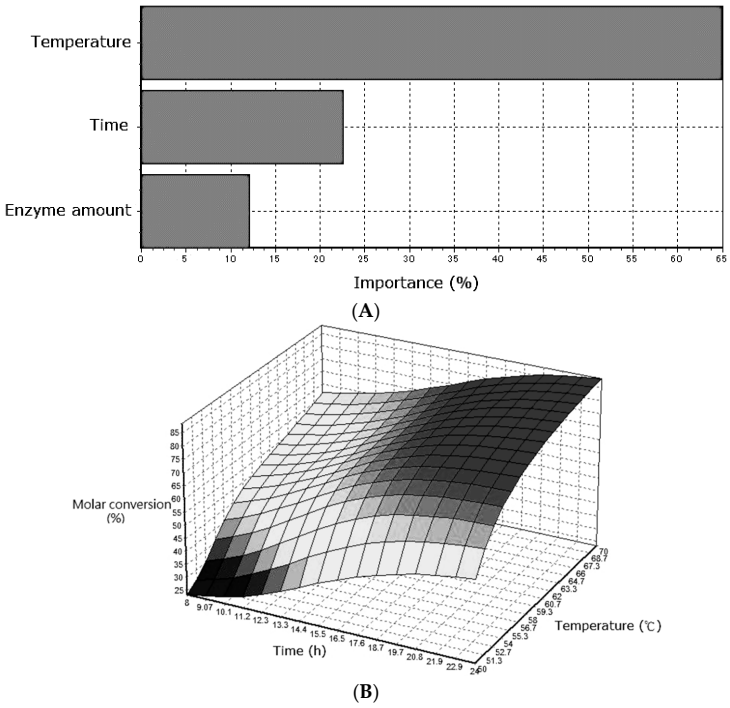


Figure 5. Influence of experimental variables on enzymatic synthesis of 2-ethylhexyl salicylate. (**A**) Importance of experimental variables in 2-ethylhexyl salicylate synthesis. (**B**) The relationships between the molar conversion of 2-ethylhexyl salicylate and reaction parameters (time and temperature).

Table 2. Validation of ANN-predicted synthesis data of 2-ethylhexyl salicylate.

Time (h)	Temperature (°C)	Enzyme Amount (PLU)	Relative Conversion (%)	
			Experimental	ANN-Predicted
10	55	600	32.0	32.7
12	55	700	42.1	42.2
14	55	800	57.9	54.1
20	65	900	81.8	85.1
23.1	66.5	881	88.2	87.0

2.3. Enzyme Reusability

To understand the enzyme reusability, the repeated use of immobilized lipase for 2-ethylhexyl salicylate synthesis was also investigated under optimal conditions. The immobilized lipase could be recovered from the reaction medium after the reaction, and then reused in the next batch. As shown in Figure 6, the relative conversion of 2-ethylhexyl salicylate still remained at about 86% after five repeated recoveries and uses. Overall, the results demonstrated that the lipase could be effectively applied for 2-ethylhexyl salicylate synthesis in the present study.

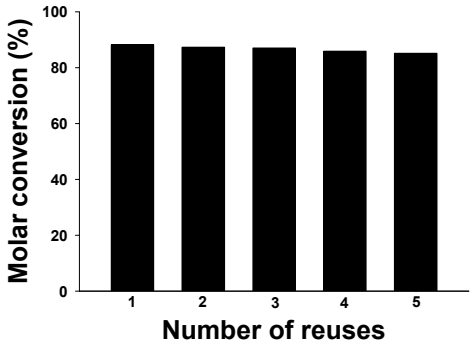


Figure 6. Reusability of the immobilized lipase on the synthesis of 2-ethylhexyl salicylate. Reusability was evaluated under the experimental conditions including a reaction time of 23.1 h, a reaction temperature of 66.5 °C, and an enzyme amount of 881 PLU.

3. Materials and Methods

3.1. Materials

Immobilized lipase Novozym®435 was purchased from Novozymes A/S (Bagsvaerd, Denmark). Methyl salicylate and 2-ethyl hexanol was purchased from Sigma-Aldrich (St. Louis, MO, USA). Other chemicals and reagents used were of analytical reagent grade or the highest purity available.

3.2. Synthesis of 2-Ethylhexyl Salicylate

All reagents were dehydrated by molecular sieves (4 Å) for 24 h before use. Briefly, methyl salicylate (13 μL, 0.1 mmol) and various amount of Novozym®435 were mixed with 2-ethyl hexanol (1 mL, 6.4 mmol) in fingernails emissions glass flask of EYELA Rotary evaporator N-1100 (Tokyo, Japan). The reaction mixture were initially operated at 80 rpm and a vacuum degree at 560 torr under different reaction times (8–24 h), reaction temperatures (50–70 °C), and enzyme amounts (500–1000 PLU). At the end of the reaction, the liquid samples from the reaction mixture were further withdrawn for determination of 2-ethylhexyl salicylate using high-performance liquid chromatography (HPLC). Analysis was performed by injecting 20 μL of the reaction mixture into the HPLC (Hitachi L-7400, Tokyo, Japan) equipped with an ultraviolet (UV) detector and a Thermo C18 column (250 mm × 4.6 mm, Agilent, Waltham, MA, USA). All separations were carried out by a

gradient elution with a 0.1% acetic acid solution and 100% methanol from 50% to 100% methanol in 3 min and then elution at 100% methanol held for 7 min. The flow rate was set at 1.0 mL min^{-1}, and the UV light was detected at 307 nm. The HPLC result is illustrated as Figure 7. The molar conversion was defined as (mmol of 2-ethylhexyl salicylate production per mmol of initial methyl salicylate) × 100%.

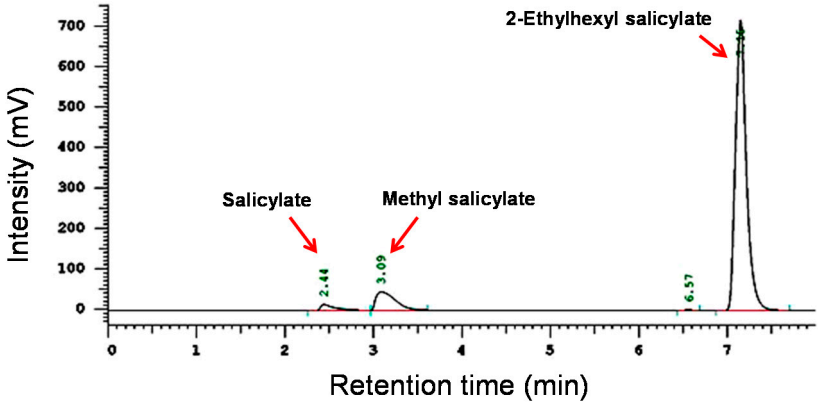


Figure 7. High-performance liquid chromatography (HPLC) chromatogram of 2-ethylhexyl salicylate.

3.3. Box–Behnken Design

A 3-level-3-factor Box–Behnken design (BBD) was employed in the present study, requiring 15 experimental runs, which were performed in a totally random order to avoid bias. The variables and their levels selected for the study of 2-ethylhexyl salicylate synthesis were as follows: reaction time (8–24 h), reaction temperature (50–70 °C), and enzyme amount (500–1000 PLU), which were listed as shown in Table 1. Three replicas were carried for each experimental point. Statistical parameters including coefficient of determination (R^2) and root-mean-square error (RMSE) were respectively calculated by Equations (1) and (2):

$$R^2 = 1 - \frac{\sum_{i=1}^{n}\left(Y_{pre} - Y_{exp}\right)^2}{\sum_{i=1}^{n}\left(Y_m - Y_{exp}\right)^2} \quad (1)$$

$$\mathrm{RMSE} = \sqrt{\frac{\sum_{i=1}^{n}\left(Y_{pre} - Y_{exp}\right)^2}{n}} \quad (2)$$

where Y_{pre} is the predicted yield of 2-ethylhexyl salicylate, Y_{exp} is the experimental yield of 2-ethylhexyl salicylate, Y_m is the average experimental yield of 2-ethylhexyl salicylate, and n is the number of experiments.

3.4. Process Optimuzation by Artificial Neural Network (ANN)

In this study, a type of feed-forward ANN, multilayer perceptron (MLP) was used to model the lipase-catalyzed synthesis of 2-ethylhexyl salicylate under both solvent free and vacuum conditions. The regression of neural network was constructed from our experimental responses by Neural Power software (Professional version 2.5, CPC-X Software, 2004) operation. Basically, the proposed ANN modeling was composed of three layers, including an input layer, a hidden layer, and an output layer, respectively [36]. In this study, it was decided that one hidden layer in the neural network was enough to solve most of the problems. However, more hidden layers might lead to an over-fitting problem. Additionally, the input layer of the proposed neural network had three neurons (nodes), characterized respectively by experimental design parameters, namely reaction temperature, enzyme amount, and reaction time. The output layer had one neuron, which represented the experimental response of molar conversion of 2-ethylhexyl salicylate. Finally, the number of hidden neurons in the

hidden layer, the ANN learning algorithms, the ANN transfer functions (nonlinear) for the hidden layer and the output layer, and the experimental repetition were determined so that the best neural network for process optimization could be modeled.

4. Conclusions

The present study demonstrated for the first time that the immobilized *C. antarctica* lipase could be well used to synthesize 2-ethylhexyl salicylate. The artificial neural network (ANN) was applied to the experimental model for optimization of the synthesis parameters. The ANN model for the 2-ethylhexyl salicylate synthesis was built and was good in data fitting and prediction. A green synthesis of cosmetic chemical, 2-ethylhexyl salicylate, in a solvent free and reduced pressure evaporation system was successfully developed, which is well modeled and optimized by ANN methodology. Overall, this study efficiently utilizes a green technology to generate 2-ethylhexyl salicylate products, which could be well applied in the cosmetic industry.

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Conflicts of Interest: The authors declare no conflict of interest.

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