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Continuous ion-exchange resin catalysed esterification of eugenol for the optimized production of eugenyl acetate using packed bed microreactor

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A green scalable flow-synthetic process for the production of eugenyl acetate, an eugenol derivative with potential applications in food and medicinal chemistry, was developed. Through batch experiments, the anion-exchange resin *Amberlyst A-21* was recognized as the suitable catalyst for the esterification of eugenol with acetic anhydride. Next, the process was switched from batch- to flow-mode by using a packed-bed microreactor integrated in an instrumental platform that permitted at the same time the continuous control the main process parameters (flow rate, feeding mixture composition, temperature) and the on-line HPLC analysis of the reactor effluent. Thanks to this apparatus, a number of experiments with different reaction conditions have been easily performed to evaluate the effects of temperature and reagents molar ratio on the eugenyl acetate production. The results have been used to carry out a central composite rotatable experimental design (CCRD) whose derived response surface model (RSM) suggested optimal temperature and acetic anhydride to eugenol molar ratio of 95 °C and 3:1, respectively. The goodness of these theoretically deduced parameters has been experimentally confirmed obtaining, with a flow rate of 40 µL.min^{-1}, a 95% conversion. The *Amberlyst A-21* packed-bed microreactor also demonstrated a good long-term stability ensuring, under the above optimized conditions, a high and stable conversion (over 93%) for prolonged reaction time.

Introduction

The continuous expansion of the demand for safe and natural products has increased interest among researchers in using essential oils as natural additives for food, cosmetics and pharmaceuticals. The reason is that they can replace different kinds of chemical additives, thanks to the properties displayed by their components. As for many other biological active natural products, even for essential oils intensive studies have been conducted in order to identify simple and safe strategies for the preparation of semi-synthetic derivatives with enhanced properties.[1] The esterification of hydroxylated bioactive compounds is probably the most common transformation adopted to modulate activity and stability,[4-7] as demonstrated by, e.g., the historical example of aspirin, the first semi-synthetic drug based on a natural product. Eugenol (4-allyl-2-methoxyphenol) is the major constituent of several important essential oils such as clove, pimento berry, bay, nutmeg and cinnamon oil. It is commonly used as a fragrance and flavouring agent in a variety of cosmetics, pharmaceuticals and food products. Eugenol has shown antimicrobial, antioxidant, anti-inflammatory, antispasmodic, antidepressant, antigenotoxic, and anticarcinogenic properties.[8,9] However, the efficiency of this compound in therapeutic treatments is limited by its poor water solubility and chemical instability.[10]

Among the strategies to increase the therapeutic efficacy of eugenol via chemical modification, the esterification of the hydroxyl group appears the simplest and the most promising one. Indeed, esters of eugenol bearing either aliphatic, aromatic or heteroaromatic acyl groups (Table 1) have been synthesized and introduced as potential future drugs against many diseases.[8-9] For instance, the simple eugenyl acetate derivative showed an increased stability[12] and exhibited its potential as antimicrobial against Gram-positive and -negative bacteria,[13,14] as well as antileishmanial therapeutic agents.[15] In addition, it has been proposed also as eco-friendly larvicidal compound against larvae of *Aedes aegypti* with lower toxicity and increased activity than eugenol.[16]

Finally, like eugenol, eugenyl acetate has been authorized for use in foods by the Joint Expert Committee on Food Additives (JECFA)[17] and the European Food Safety Authority (EFSA)[18] and it is currently listed in the European Union database of flavouring substances.

In recent years, several eugenol esters have been prepared following either biocatalytic or chemical approaches (Table 1). Apart from the recent use of the solid super acid modified zirconium

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UDCaT-5,[11] all the chemical catalysed transformations were performed through homogeneous acid or basic catalysis. Even if these conditions are the most employed for the esterification of natural products, such processes have been developed with the purpose of maximizing product yield, without considering the environmental impact of inorganic waste produced during the separation stage of the process, when a typical water quench and neutralization (for acidic or alkaline systems) is needed. Driven by an increasing demand for greener chemistry and technology, efforts have been made to develop environmentally friendly, yet cost effective processes for esterification reactions. In recent years, a great deal of attention has been focused towards the use of supported catalysts[19,20] that not only can be easily recovered and reused but have also favoured the development of continuous flow processes for a number of industrially important productions.[21,22] Most of the articles or patents describing the esterification of natural products promoted by heterogeneous catalysts, falls in the field of biofuels production[23-26] and, in several cases, ion-exchange resins have been successfully employed as acid[27,28] or basic catalysts.[29]

Based on all these promising features, the aim of this work was to set up an optimized continuous-flow process for eugenyl acetate production based on the use of an ion-exchange resin as catalyst and acetic anhydride as acylating agent. A preliminary study conducted under batch conditions allowed to identify the *Amberlyst A-21* as the suitable catalyst. This was used to prepare a packed-bed microreactor where the continuous-flow eugenyl acetate production was optimized. The assessment of optimal process variables (i.e., flow rate, reagent molar ratio and temperature) was carried out through experimental design and response surface methodology.[30,31] Moreover, the operational stability of the catalyst was examined in order to assess its potential use for commercial application.

Results and discussion

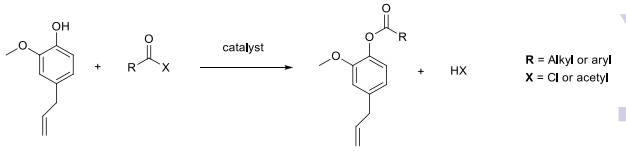
Experiments in batch conditions

Based on the current literature,[27,28] the ion-exchange resins *Amberlyst A-21* and *Amberlite IR120* were identified as potential catalysts for the esterification of eugenol. Experiments in batch mode were conducted in order to verify their efficiency. The results reported in Table 2 show that the highest conversions were obtained using *Amberlyst A-21*. It was also evident that the excess of acyl donor contributed to increase the eugenyl acetate production. Indeed, by using a 1:5 eugenol to acetic anhydride molar ratio, both catalysts afforded approximately quantitative conversions. Taking into account these results, further studies were carried out using the anion exchange resin *Amberlyst A-21* as catalyst.

Optimization of continuous esterification of eugenol in a fixed bed microreactor

The continuous production of eugenyl acetate was carried out using the experimental apparatus represented in Figure 1. The system consists of two binary HPLC pumps, one of which feeds the packed bed microreactor with adjustable ratios of eugenol and acetic anhydride, while the other is connected to an analytical chromatographic column (C18 reversed-phase) for the on-line monitoring of the process.

Table 1. Eugenol esters derivatives and synthetic conditions.



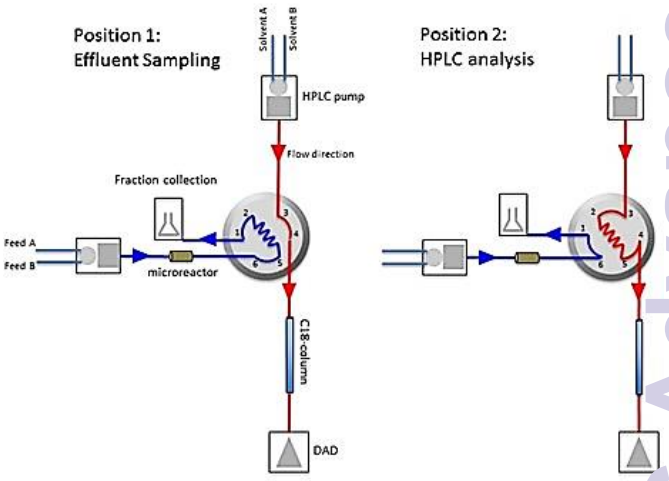
R	X	Catalyst	Reference
Phenyl	Cl	NaOH	8, 9
Phenyl	OH	UDCaT-5	11
n-alkyl chain (C11-C15)	Cl	NaOH	8
Cyclic alkyl	Cl	NaOH	10
Pyridyl	Cl	Pyridine	10
Methyl	Acetyl	None	12
Methyl	Acetyl	Novozym 435	13, 14
Methyl	Acetyl	Amberlyst A-21	This work

Table 2. Results of eugenyl acetate conversion for the preliminary tests in batch mode.[a]

Resin[b]	Molar Ratio[c]	Conversion (%)[d]
Amberlyst A-21	1:5	100
	1:3	89
	1:1	78
Amberlite IR120	1:5	99
	1:3	68
	1:1	38

[a] Reaction conditions: solvent-free system, 2 h, 50 °C, orbital shaking 120 rpm. [b] 20% (w/v). [c] Eugenol to acetic anhydride. [d] Determined by HPLC analysis.

Figure 1. Scheme of the experimental set up employed to monitor reaction progress.



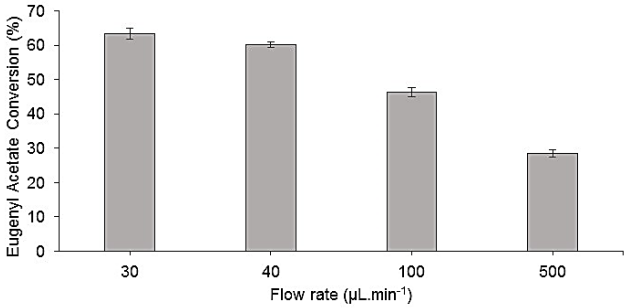
The two lines are connected by a remotely-controlled multiport valve, which allows for the sampling of microreactor effluent at determined times. Besides automation, the instrumental platform allows for a flexible control of experimental conditions (such as, the

easy modification of the mixture composition feeding the microreactor).

Effect of flow rate

Our optimization study started from the investigation of the effect of flow rate (or residence time, RT) on reaction conversion. This parameter is particularly important in flow chemistry as it is commonly acknowledged that if, on the one hand, low flow rates (allowing for longer RTs) favour conversion, on the other way it negatively impact production yield. Therefore, a compromise between RT/conversion has to be found. The results of this study are reported in Figure 2, where eugenyl acetate conversion is plotted as a function of flow rate. As it can be seen by the plot, a flow rate of 40 μL.min^{-1} represents a satisfactory starting point for further optimization studies as it allowed obtaining both reasonable conversion (60%) and RT (29 min). The gain of conversion achievable at the cost of reducing the flow rate at 30 μL.min^{-1} is too small (only about 3%) in comparison to the corresponding increase of RT (+35%). On the other hand, the study of high-flow rate regime, showed that conversion decreased rapidly with increasing the flow rate (it is only about 45% at 100 μL.min^{-1} and even smaller than 30% at 500 μL.min^{-1}) to make these conditions competitive.

Figure 2. Effect of flow rate on eugenyl acetate production.



Reaction conditions: eugenol to acetic anhydride molar ratio 1:5 and 50 °C.

Experimental design

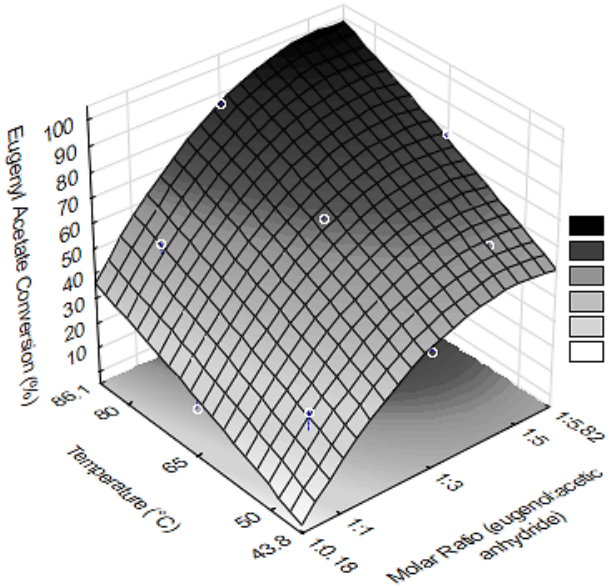
Based on the previously obtained results, a 2^2 central composite rotatable experimental design (CCRD) with triplicate repetitions of the central point[30,31] was carried out to evaluate the effect of temperature and reagent molar ratio on reaction conversion at constant flow rate (40 μL.min^{-1}). Table 3 presents the matrix of the experimental design. Eleven experiments were performed, nine of them (runs 1-9) with different combinations of temperature/reagent molar ratio, while the experiments from the central point of the planning design (runs 9, 10 and 11) were conducted at the same temperature (65 °C) and with the same eugenol to acetic anhydride molar ratio (1:3). The conversion percentage reported in Table 3 are referred to the steady-state conditions that, as shown by Figure 3, were reached after about 1.5 h. Highest steady-state conversions (91% and 86%) were obtained in runs 4 and 8, at temperature of 80.0 and 86.1 ºC and eugenol to acetic anhydride molar ratio of 1:5 and 1:3, respectively. The experimental points obtained for runs 9, 10 and 11 allowed to verify the excellent reproducibility of the experimental data. A high selectivity in the continuous esterification of eugenol with *Amberlyst A-21* in a fixed bed microreactor could also be observed, since the formation of by-products in all experiments was not observed.

Successively, data obtained from the experimental design were analysed by response surface methodology with the scope of finding a semi-empirical correlation for conversion as a function of temperature and eugenol to acetic anhydride molar ratio. This study led to the following equation:

$$C = 66.61 + 20.22 \times MR - 9.54 \times MR^2 + 15.10 \times T - 0.71 \times T^2 + 1.19 \times MR \times T \quad (1)$$

where C represents the conversion of eugenol to eugenyl acetate (%), T is the temperature (ºC) and MR the eugenol to acetic anhydride molar ratio. The analysis of variance (ANOVA) was used to assess the goodness of fit of the model. Based on F-test, the conclusion can be drawn that the model is predictive. In fact, the calculated F value is about fifteen times larger than the tabular F ($F_{calculated}$=77.5 vs. $F_{0.95;5;5}$=5.05) with a regression coefficient satisfactory enough (0.987). Therefore, the model expressed by Equation (1) was used to generate the response surface of Figure 3 and to predict the effects of experimental conditions on eugenyl acetate production (column 5 of Table 3). Results of experimental design and data of Table 3 suggest not only that it is not convenient to use an eugenol to acetic anhydride molar ratio lower than 1:3 but also that with this composition the conversion can be significantly enhanced by increasing temperature.

Figure 3. Response surface of eugenyl acetate conversion as a function of temperature and eugenol to acetic anhydride molar ratio.



Experimental data and conditions shown in Table 3.

Based on this information, the temperature was increased from 85 to 95 °C, by keeping the feeding composition constant (eugenol to acetic anhydride molar ratio equal to 1:3). Figure 4 shows indeed that increasing temperature favours the conversion. Remarkably in agreement with the proposed model, at 95 °C, the conversion was 95%.

Operational stability of Amberlyst A-21

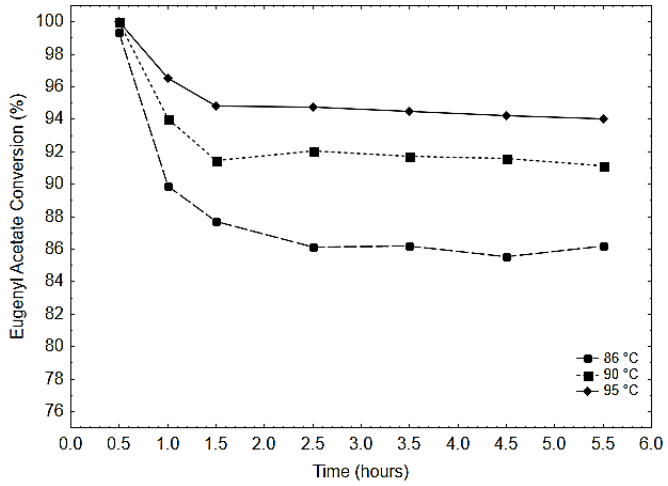
The stability of the catalyst was detailed investigated, as this is a key parameter for evaluating its potential for industrial scale continuous esterification processes. High operational stability for ion-exchange-resin-based (micro)-reactors has been already observed in various continuous flow processes, such as the esterification of acidified oil with methanol[32] and the ketalization of glycerol.[33-35] To assess the stability of *Amberlyst A-21*, the following conditions were employed: eugenol to acetic anhydride molar ratio of 1:3, feed flow rate 40 µL.min^{-1} and temperature 95 °C. As demonstrated in Figure 5, eugenyl acetate conversion was practically constant (over 93%) during the entire observation time (32 h) showing thus the excellent operational stability of the catalyst.

Table 3. Matrix of the experimental design (coded and real values) with responses in terms of eugenyl acetate conversion.

Run	Molar Ratio[a]	Temperature (°C)	Experimental Conversion (%)	Predicted Conversion (%)	RED (%)[b]
1	-1 (1:1)	-1 (50.0)	27	22	16.64
2	1 (1:5)	-1 (50.0)	59	60	-1.65
3	-1 (1:1)	1 (80.0)	53	50	6.16
4	1 (1:5)	1 (80.0)	91	93	-2.35
5	-1.41 (1:0.18)	0 (65.0)	14	19	-35.57
6	1.41 (1:5.82)	0 (65.0)	79	76	3.38
7	0 (1:3)	-1.41 (43.8)	42	44	-4.73
8	0 (1:3)	1.41 (86.1)	86	86	-0.39
9	0 (1:3)	0 (65.0)	67	66	0.20
10	0 (1:3)	0 (65.0)	66	66	-0.09
11	0 (1:3)	0 (65.0)	66	66	-0.07

[a] Eugenol to acetic anhydride. [b] Relative error deviation - RED = $\left(\frac{C_{exp}-C_{pred}}{C_{exp}}\right)x100$.

Figure 4. Evaluation of the effect of temperature on eugenyl acetate production.



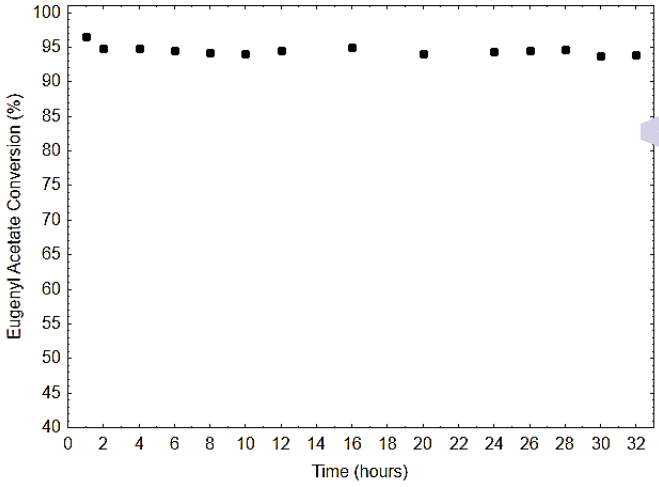
Experimental conditions: eugenol to acetic anhydride molar ratio of 1:3, flow rate of 40 µL.min^{-1}, and temperature of 86, 90 and 95 °C.

Experimental

Materials

The substrates used in the esterification reactions were commercial eugenol (Aldrich, 99% purity) and acetic anhydride (Riedel-de Haën, 99% purity). Analytical standard of eugenyl acetate is commercially available from Fluka. As heterogeneous catalysts the following materials were employed: *Amberlite IR120* hydrogen form (cation exchange resin; physical form: beads; matrix: styrene divinylbenzene copolymer; matrix active group: sulfonic acid; particle size: 620-830 µm; operating pH: 0-14; capacity: 1.8 meq·min^{-1} by wetted bed volume; maximum operating temperature 121 °C) and *Amberlyst A-21* (anion exchange resin; physical form: beads; matrix: styrene divinylbenzene (macroporous); matrix active group: alkyl amine; particle size: 490-690 µm; operating pH: 0-14; capacity: 1.3 meq·min^{-1} by wetted bed volume; maximum operating temperature 100 °C). Both catalysts were from Sigma-Aldrich. HPLC grade methanolwas also from Sigma-Aldrich. Before all experiments, resins were dried in oven at 100 °C for 24 hours.

Figure 5. Evaluation of operational stability of *Amberlyst A-21*.



Experimental conditions: eugenol to acetic anhydride molar ratio of 1:3, temperature of 95 °C and flow rate of 40 µL.min^{-1}.

Experiments in batch conditions

Solvent-free batch reactions were carried out in 2 mL-tube with orbital shaking (120 rpm) at 50 °C. In all experiments the eugenol/acetic anhydride molar ratio was 1:5, resin concentration was 0.2 g.g^{-1} (based on substrates) and reaction time 2 hours. After each experimental run, the resin was separated from the reaction medium and product quantification was performed by High-performance Liquid Chromatography (HPLC).

Quantification of eugenyl acetate by HPLC

Quantification was carried by means of calibration curves built with standard solutions of eugenol and eugenyl acetate in the range of 0-25 mM and 0-33 mM, respectively.

In order to validate the method, parallel analyses were carried out by ^{1}H-NMR analysis dissolving the sample mixture (10 µL) in deuterated chloroform (1 mL). The signals of the methoxy groups of eugenol (singlet ta 3.97 ppm) and eugenyl acetate (singlet ta 3.80 ppm) were considered and the conversion was calculated from the ratio between the integral of the product signal and the sum of the integrals of product and substrate signals.

Continuous esterification of eugenol in packed bed microreactor

Preparation of the microreactor

Microreactor was prepared by gravity packing. A 10-cm long chromatographic column (0.46 cm internal diameter) was used. 514 mg of resin *Amberlyst A-21* were necessary to fill the column. The packed bed void fraction (ε), calculated according to Shang et al.[36], was 0.58 mL.

Experimental apparatus and procedure

Reaction progress was monitored by using the experimental set up shown in Figure 6. This consists of two binary HPLC pumps (Agilent 1100 series, Agilent Technologies) connected through a remotely controlled 2-position 6-port switching valve (Rheodyne). One capillary pump (first dimension) feeds the microreactor with adjustable ratios of eugenol and acetic anhydride. The microreactor was placed in a thermostatic bath (Grant – TC 120) with controlled temperature (±0.1 °C) and its outlet was connected to a fraction collection system, or to waste depending on need. The second pump (second dimension) delivers a mobile phase made of a binary mixture of methanol:water (70:30, v/v) to a chromatographic column (C18-RP Symmetry from Waters, 15×0.21 cm ID, particle size: 3.5 µm), after which a diode-array detector (DAD, Agilent 1100 series) is placed. The flow rate on the second dimension was 0.1 mL.min^{-1} and the chromatographic column was thermostated at 30 °C. The microreactor effluent can be sampled by means of the multiport valve, (loop between port 2 and 5) and redirected to the chromatographic column for eugenol and eugenol acetate quantification.

This bi-dimensional experimental platform has been particularly convenient for monitoring the flow-mode esterification of eugenol. Indeed the microreactor outlet was directly analyzed on the second dimension without need of dilution and sample handling. One µL of the microreactor effluent was sampled (Figure 2, position-1) at given times and injected in the C18 column (Figure 2, position-2). The detector was calibrated so to avoid detector saturation (both product and reagent were monitored at 302 nm). The composition of the mobile phase (methanol:water 70:30, v/v) allows for both an easy dissolution of the organic sample coming from the microreactor and a timely chromatographic separation of unreacted eugenol from eugenyl acetate.

Effect of flow rate

The effect of flow rate was evaluated by performing a series of experiments at different flow rates (500, 100, 40 and 30 µL·min^{-1}) keeping constant the temperature (50 °C) and feed concentration (eugenol/acetic anhydride molar ratio 1:5). At each flow rate, reaction conversion was measured under steady-state conditions. Residence times were calculated as described by Dalla Rosa et al.[37] At flow rates of 500, 100, 40 and 30 µL.min^{-1}, residence time was, respectively, 2.3, 11.6, 29.0 and 38.7 min.

Optimization of eugenyl acetate production: effect of substrate concentration and temperature

A 2^2 Central Composite Rotational Design (CCRD) was carried out. Eugenol to anhydride acetic molar ratio was varied from 1:0.18 to 1:5.82 and temperature from 43.5 to 86.1 °C. Flow rate was 40 µL.min^{-1}. In all experiments, reaction was monitored for 5.5 hours. For statistical analysis of experimental design, the mean conversion of four steady-state points (2.5, 3.5, 4.5 and 5.5 h) of each run was calculated. The center point of the design was repeated three times in order to allow a better estimate of the experimental error and to provide extra information about the significance of effects.[30] All results were analyzed using Statistica® 8.0 (Statsoft Inc., Tulsa, OK, USA), considering a significance level of 95% ($p<0.05$). Based on the information from experimental design, the effect of temperature was evaluated with a molar ratio of eugenol to acetic anhydride of 1:3. In these experiments, the following temperatures were considered: 86, 90 and 95 °C.

Operational stability of Amberlyst A-21

To assess reaction operational stability, 32 hours experiments were performed under optimized conditions (i.e., 1:3 eugenol / acetic anhydride molar ratio, 95 °C temperature and 40 µL.min^{-1} flow rate).

Conclusions

The anion exchange resin *Amberlyst A-21* proved to be a very efficient catalyst for the flow-mode production of eugenyl acetate from eugenol and acetic anhydride. Thanks to a Central Composite Rotational Design, a response surface model has been built to predict the optimal parameters for the in-flow eugenyl acetate production. Experimental results perfectly fitted with the model and an optimized conversion of eugenol to eugenyl acetate of 95% was reached. The catalyst did not show loss of activity and the above conversion was ensured during 32 hours of continuous esterification. The notable features of this method are simplicity in operation, short reaction time, cleaner reaction profiles, low cost, high stability and reusability of the catalyst, easy of scaling up (for instance by simply operating in parallel multiple microreactors) and very good to excellent product yields. In conclusion, we have designed and optimized a complete, new, heterogeneous green process for the continuous synthesis of eugenyl acetate.

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