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Dimethyl Fumarate: Heterogeneous Catalysis for the Development of an Innovative Flow Synthesis

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ABSTRACT: The present work describes the development of an improved synthesis of the active pharmaceutical ingredient (API) dimethyl fumarate. The use of continuous flow technology and the newly developed methylation conditions solve some of the issues of previous commercial production strategies, *e.g.*, reaching complete conversion and avoiding the formation of toxic impurities. The optimization was carried out using the design of experiment approach and afforded a very efficient, sustainable process, suitable for the industrial application.

KEYWORDS: dimethyl fumarate, flow synthesis, continuous esterification, heterogeneous catalysis, design of experiment

INTRODUCTION

After decades when continuous flow (CF) processing has been an essential technology in petrochemical and bulk chemical industries, in recent years, it became a major focus for process development also in the pharmaceutical sector. The academic efforts in this area grew a lot as well as the number of patents applications from industrial R&D groups.^{1–3}

The number of examples of CF processes (or part of processes) in the pharmaceutical industry is continuously increasing. In many cases, a shift from existing batch processes to CF manufacturing is reported, but, more recently, many industrial syntheses are directly developed in CF. Even if not applicable in all sections of a production process, CF manufacturing can have numerous advantages over traditional batch processes. The well-known benefits of flow manufacturing include: (i) precise control of reaction conditions due to efficient heat and mass transfers; (ii) high reaction reproducibility; (iii) the possibility of exploring reaction conditions not easily achievable in batch (e.g., superheating conditions); (iv) the possibility of system automation; (v) safer handling of hazardous reagents; and (vi) a decreased reactor footprint.⁴ This last aspect is of particular interest in the emerging field of ondemand active pharmaceutical ingredient (API) production.⁵

Among the huge number of chemical transformations and technological configurations, the use of heterogeneous catalysis in CF synthesis is a very well-known and efficient approach.⁶ In one of the possible configurations, the catalyst is contained in a columnar reactor (packed-bed reactor) and the reaction solution is passed through the catalyst. Given the simple reactor typology, this method is the most widely used and represented in the literature; this is particularly true for industrial applications, where it is privileged to avoid the introduction of additional operations to separate the catalyst from the target product. Under these conditions, it is possible to achieve high efficiency and to obtain fast transformations, exploiting the high ratio between the amount of catalyst and substrate processed in the time unit.

Dimethyl fumarate (DMF) has recently attracted attention in the treatment of psoriasis and multiple sclerosis. DMF can be seen as a prodrug, with the corresponding monomethyl ester being the active molecule (monomethyl fumarate (MMF); Figure 1).^{7,8}



Figure 1. Dimethyl fumarate (DMF) and monomethyl fumarate (MMF)

DMF was marketed in 1994 (Germany) for use in systemic psoriasis treatment and it was also launched in 2013 for the treatment of adults with relapsing forms of multiple sclerosis. In 2017, an oral DMF formulation was approved in Europe for the treatment of moderate-to-severe plaque psoriasis in adults.

Although the mechanism of action is not yet well understood, the main activity of DMF and MMF is supposed to be immunomodulatory by reducing the expression of micro-RNA-21, which is essential for the production of pathogenic cells in multiple sclerosis and psoriasis.⁹

There are no active patents covering the product itself and preventing the production of DMF. From the process point of view, besides specific limitations related to purification protocols,^{10–12} the only limitations are related to specific particle size distributions (PSD) that can be obtained using special technologies in the phase of isolation.^{13,14} This fact,

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entrya	catalyst	temp (°C)	time (h)	pressure (bar)	%FA ^b	%MMF ^b	%DMF ^b
1	H ₂ SO ₄ (0.22 mmol)	130	4	8.1	0.10	5.09	94.81
2	H ₂ SO ₄ (0.43 mmol)	90	48		0.00	0.67	99.33
3	Mont K10 (1.00 g)	90	42		91.47	4.13	4.40
4	SCX-2 (10% mol)	110	5.5	5.5	0.00	1.68	98.32
5	SCX (10% mol)	110	5.5	5.5	0.11	4.86	95.02
^a Experiment 1 A%.	run in MeOH on 1.0 g of FA	. (8.6 mmol) and D	MC (40.0 mmo	l). ^{<i>b</i>} Determined by hig	h-performance	liquid chromatog	graphy (HPLC)

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Table 1. Catalyst Batch Screening

together with the annual worldwide consumption (which in 2019 was over 25 tons, corresponding to over \$5000M of sales),¹⁵ makes DMF a good candidate for API manufacturers, in particular for the generic market. DMF market will probably be only marginally eroded by the newly developed and approved successor, diroximel fumarate (1-[2-(2,5-dioxo-1-pyrrolidinyl)-ethyl] 4-methyl (2*E*)-2-butenedioate),^{16,17} a nonsymmetric diester of fumaric acid (FA), again a prodrug of MMF.

The most common and most straightforward process for the production of DMF is the acid-catalyzed esterification of FA in the presence of methanol (MeOH). The reaction reaches an equilibrium, and it is usually driven to complete conversion by distillation of most part of the solvent, removing the formed water and increasing the concentration. This approach presents positive aspects (*e.g.*, cheap substrate and reagents) as well as various drawbacks:

- (1) Long cycle time, for reaction and distillation of part of the solvent;
- (2) Use of mineral acids, usually sulfuric acid or hydrochloric acid, as catalyst in the presence of MeOH, with the possible formation of carcinogenic byproducts (*e.g.*, dimethyl sulfate or methylchloride), that request specific purification, usually involving water, to reduce their content below the limits imposed by ICH guidelines.¹⁸

Over time, different strategies were developed for the production of DMF, exploiting different catalysts, in some cases using different raw materials (*e.g.*, maleic anhydride)¹⁹ and also using the CF technology.^{20,21} In most cases, these alternative strategies do not fully address the reported drawbacks and their actual industrial advantage can be considered really limited.

Moreover, the landscape of the possible alternative approaches is limited by the relatively low market price of the final API, which forces to find and develop very efficient processes, which should avoid the introduction of additional costs, deriving from the use of special raw materials, reagents, and catalysts.

Our efforts to develop a new more efficient process for the synthesis of DMF were focused on:

- (a) Replace mineral acids as catalyst for the esterification, avoiding the formation of undesired byproducts;
- (b) Develop a flow process characterized by high conversion and efficiency, affording DMF at competitive costs;
- (c) Use of a heterogeneous catalyst, stable at high temperature and pressure, suitable for the production of APIs;
- (d) Use of a cheap and safe water scavenger, to drive esterification to complete conversion.

RESULTS AND DISCUSSION

Solvent and Catalyst Selection. As previously described, there is a strong need to find proper reaction conditions for

esterification of FA, to achieve the desired high conversion and change mineral acids as catalysts. Considering a possible alternative solution for both aspects, we needed to avoid the introduction of expensive components, to achieve an industrial process that could compete with the original one in terms of production costs.

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One of the most straightforward strategies to drive Fisher esterification to completion is the removal of water from the reaction mixture. With the final target of developing a flow process, we considered water scavenging. In particular, among different possible scavengers for water in MeOH solution, dimethylcarbonate (DMC) was selected as a cheap, nontoxic, and industrially available material, used as a reagent in methyl ester formation.²² DMC can readily react with water to give MeOH and CO₂. The ratio between methanol and DMC was set at 1:3 v/v with an FA concentration of 5% w/v, taking into account process productivity, the generally low solubility of FA, and setting a suitable ratio to remove the water formed during the process.

The selection of possible alternative catalysts was mainly focused on heterogeneous catalysts, which can acquire significant benefits from CF conditions.⁴ In particular, heterogeneous-acid-catalyzed esterification of carboxylic acids with MeOH or other alcohols is widely reported in the literature.^{23–29}

The most common supports used in this field are polystyrenebased resins bearing sulfonic groups;³⁰ however, the use of such resins is usually not recommended in APIs production due to the possible presence of residual styrene monomer, whose major *in vivo* metabolite styrene-7,8-oxide is classified as probably carcinogenic to humans and carcinogenic to rodents.³¹

For this reason, polystyrene-based catalysts were not considered in this study and some commercially available heterogeneous catalysts were screened: montmorillonite K10 and two silica-based materials, SiliaBond Propylsulfonic Acid (SCX-2) and SiliaBond Tosic Acid (SCX).

The screening experiments were performed in batch mode, using a mixture of MeOH and DMC at different temperatures, also under superheating conditions (Table 1). Two reference experiments (entries 1 and 2) were performed using sulfuric acid. The results clearly indicated that Montmorillonite K10 is not active under these conditions, whereas silica-supported SCX-2 is the most efficient catalyst, among the tested ones, affording more than 98% conversion to DMF at 110 °C in less than 6 h.

For this reason, SiliaBond Propylsulfonic Acid (SCX-2) was selected for the following development. Besides the absence of undesired residues of problematic monomers, the advantages of silica-supported catalysts include: (i) no swelling, (ii) fast kinetics, (iii) solvent independence, (iv) good mechanical stability, and (v) thermal stability.³²

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Figure 2. (a) Feed as suspension; (b) feed as solution; and (c) feed as superheated solution.

CF Setup. Once catalyst and solvent composition were selected, the CF setup was studied. The packed-bed reactor configuration, where a heterogeneous catalyst is simply packed into a columnar reactor and the reaction solution is passed through the catalyst, is one of the most simple configurations for the use of heterogeneous catalysts in CF. The main limitation of this configuration is posed by the fact that it can be used only if the reaction mixture is a solution throughout the whole process.

As FA is characterized by very low solubility in MeOH and in MeOH/DMC mixtures, there was the need of developing a suitable procedure to obtain a solution to be submitted to the reaction with heterogeneous catalyst.

Considering that FA solubility in a 1:3 mixture of MeOH/ DMC is around 5% only at 90–100 $^{\circ}$ C, *i.e.*, above reflux temperature, and considering that the solubility of MMF and DMF is much higher in the same solvent mixture, three different possible approaches could be considered.

The first reactor configuration is shown in Figure 2a, where FA is transferred as a suspension in the MeOH/DMC mixture, using a peristaltic pump, to a coil reactor heated at 125 $^{\circ}$ C; in this phase, FA is completely dissolved, with no significant conversion to MMF and DMF. The hot solution is then passed to a glass cartridge reactor filled with the heterogeneous catalyst; this is the stage where esterification to DMF occurs.

In a second configuration (Figure 2b), the conversion of FA to DMF is performed in two steps: the first one is performed in batch mode, where FA is refluxed for 1 h in MeOH in the presence of SCX-2 catalyst (10% w/w), with a partial conversion of FA to MMF and DMF (the final composition is generally 20% of FA, 60% of MMF, and 20% of DMF; all components are

soluble in MeOH at this concentration). Afterward, the catalyst is filtered off and the obtained solution is added with DMC. The resulting solution is then pumped by means of a syringe pump into the cartridge reactor filled with SCX-2, where complete conversion to DMF is obtained.

The third configuration (Figure 2c) involves the use of a medium-pressure reservoir to dissolve FA in the solvent mixture at 90–100 °C (*i.e.*, superheating conditions). The resulting hot solution is pumped directly to the cartridge reactor filled with SCX-2.

The first and third setups could be the preferred choice for the final production applications, while the second one could be more easily standardized for laboratory-scale optimization studies. For this reason, a first set of experiments was dedicated to the comparison of the results of the CF process using the configurations described in Figure 2a,b. Table 2 reports the results of the trials: it is clear that the final conversion to MMF and DMF is similar and not influenced by the composition of the feeding mixture.

Table 2. Comparison between Suspension Feed and SolutionFeed

	$R_{t} \operatorname{column} (\min)$	T column (°C)	%FA ^a	% MMF ^a	% DMF ^a
config. 2b ^b	30	130	0.00	1.12	98.88
config. 2b ^b	20	120	0.01	2.26	97.73
config. 2a ^c	30	125	0.00	1.78	98.22
an . 1		b		200/ 10	

"Determined by HPLC A%. "Input mixture: FA 20%, MMF 60%, DMF 20%. "Input mixture: FA 100%.

In all configurations, after the back pressure regulator (BPR), set at 7 bar, gas evolution was observed, confirming the water scavenging efficiency of DMC.

With the aim of reducing possible variability coming from the use of a suspension (using a peristaltic pump, the actual amount of FA pumped could change during the experiment, whereas a syringe pump can assure more stable flow rate), optimization of the process was performed using the two-step configuration 2b: a single solution of FA/MMF/DMF was prepared and used for the following trials.

Parameters Optimization. Starting from the results reported in Table 2 and considering the maximum working temperature of 140 °C for the SCX-2 catalyst (as reported by manufacturer's product specifications), the optimization study was developed by means of design of experiment (DoE) approach.

Central composite design (CCD) was used to systemically investigate the effect and the interactions among selected independent variables on the conversion to DMF. The selected quantitative variables were:

- Temperature of the packed-bed reactor: The temperature of the reactor was controlled setting the temperature of the heating block; the small diameter of the cartridge reactor (15 mm) assures the homogeneous temperature profile across the catalyst bed;
- Residence time in the packed-bed reactor: The residence time was controlled changing the flow rate, and the volume of the reactor was maintained constant (11 mL);
- Catalyst loading: Expressed as % of pure SCX-2 present in the packed-bed reactor. To study the effect of catalyst loading, the SCX-2 catalyst was mixed with standard inert chromatographic silica gel, in variable proportions, to

change the amount of active catalyst, maintaining a constant cartridge volume. This strategy assured that the minimum amount of expensive catalyst would be used to achieve the desired results.

Since a face-centered design has been used, each factor was studied at three levels. The levels were selected according to the results of preliminary experiments, and the stability of catalyst and are reported in Table 3.

Table 3. Selected Variables and Levels for Central Composite Design

	levels		
variable	-1	0	+1
temperature (°C) T	110	120	130
residence time (min) R _t	10	20	30
catalyst loading (%) L	50	75	100

Table S1 in the Supporting Information shows the experiments (14 distinct experiments and 4 replicates of the central point, entries 15-18) and the results. The experimental responses that were recorded are FA, MMF, and DMF content. The experiments were performed in a randomized order.

The results clearly indicate that FA was completely converted in all cases and that MMF and DMF were the only components of the reaction mixtures (the sum of their A% is always 100). Consequently, the only response that was taken into consideration was %DMF (response to be maximized).

The results were analyzed using Chemometric Agile Tool (CAT).³³

From a first analysis of the results, experiment 5 (Table S1; variables levels -1, -1, -1) showed a suspiciously low response. The experiment was replicated, and the result was confirmed.

This fact suggested the presence of a "discontinuity" in the response surface in the selected domain, which would make adequate modeling impossible. For this reason, it was decided to exclude experiment 5 from the dataset.

After the exclusion of experiment 5, the experimental design was no longer symmetrical. This entailed an increase of the leverage and confidence interval in the area close to the missing point (Figure S1, Supporting Information).

Anyway, this did not affect the identification of the optimal conditions because the region of interest is at the opposite region of the chemical space. Figure 3 shows the response surface and the plot of the coefficients (together with their statistical significance).

The model is the following (eq 1)

$$Y = 97.01 + 2.75X_{1}(***) + 3.64X_{2}(***) + 1.00X_{3}(**) - 1.83X_{1}X_{2}(***) - 0.37X_{1}X_{3} - 0.02X_{2}X_{3} - 0.89X_{1}^{2} - 2.45X_{2}^{2}(***) - 0.06X_{3}^{2}$$
(1)

The effect of interactions among variables and of quadratic terms is not easy to predict from coefficients. For this reason, isoresponse surfaces for different values of the variables were generated (Figure 4 reports one of the surfaces; additional ones are reported in Figure S2, Supporting Information) to investigate the experimental domain and to identify the optimal conditions in which the percentage of DMF is at least 98%.

Even if the results of DoE could seem not unexpected (all linear coefficients have a positive effect on conversion), this

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Figure 3. Response surface and plot of the coefficients.



Figure 4. Iso-response surfaces: temperature T vs residence time R_t with catalyst loading L at -0.5 level, with semiamplitude of the confidence interval.

approach afforded in-depth knowledge of the explored chemical space.

Considering the target of 98% of conversion, it could be concluded that a sweet spot for this system is represented by the following conditions (corresponding to the red dot in Figure 4):

- Temperature *T*: 125 °C (level +0.5), 15 °C degrees lower than the temperature limit for the catalyst;
- Residence time *R*_t: 30 min (level +1), suitable to guarantee good productivity for the industrial production;
- Catalyst loading *L*: 63% (level –0.5), a good compromise to limit the amount of expensive material used in the process.

These same optimized conditions were tested both in this two-step configuration and in the suspension feed configuration, using the peristaltic pump, obtaining results in very good agreement with that predicted.

Catalyst Stability and Performance in Time. With the aim to test the catalyst stability and to assess the amount of FA that can be processed with a defined amount of catalyst, an experiment using a suspension of 200 g of FA in MeOH (1000 mL) and DMC (3000 mL) was performed. The whole experiment was run for 180 h using the same cartridge containing 4.5 g of pure SCX-2 mixed with 2.7 g of standard silica gel.

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Figure 5. Volume collected vs A% conversion to DMF.

As reported in Figure 5, the conversion to DMF was essentially constant for all of the experiment time, with no visible loss of activity.

This result showed that the catalyst is stable under the reaction conditions for a long time and that 1.0 g of pure SCX-2 is suitable for the conversion of at least 44 g of FA to DMF.

Even if it is not possible to estimate the possible run time when the catalyst would lose efficiency, the working time of 80– 100 h before catalyst replacement (the actual time range will be determined on the industrial scale) would perfectly fit with 5 days of continuous operations, corresponding to one working week.

The surface properties of both fresh and used catalyst were investigated. Table 4 summarizes the results of this investigation. It is evident that no significant modifications were introduced by the long reaction time at a high temperature and pressure.

Table 4. Surface Properties of Fresh and Used Catalysts

	fresh catalyst	used catalyst
BET surface area (m ² /g)	393	389
BJH ads cumul. pore vol. (cm ³ /g)	0.688	0.675
BJH ads average pore diameter (Å)	62	59

These observations are confirmed by SEM images of the two samples (Figure S3, Supporting Information); the images confirm that the morphology of the catalyst was not affected by the use.

All of these data confirmed that the expensive SCX-2 catalyst performed quite efficiently under the process conditions, assuring economic sustainability.

The collected solution was concentrated under vacuum to a volume of 300 mL, and MeOH was added to obtain raw DMF (>99.5% purity by HPLC and >80% yield). Avoiding the use of water for the isolation of DMF is particularly beneficial, as the distilled solvent and the mother liquors could, in principle, be recycled, to increase process efficiency.

Scale-Up Trials. After the optimization of the process parameters, the same conditions were tested in larger-scale trials.

In this case, a high-pressure peristaltic pump with a flow rate of 1.3 L/h was used (nominal productivity of this setup is 80 g/h of DMF in solution, before isolation), with a catalyst cartridge of 700 mL, filled with the optimized mixture described above. Applying the same residence time and temperature, conversion

to DMF higher than 98% was obtained for all samples collected during an 80 h experiment.

This final experiment confirmed the industrial feasibility of the final process conditions.

CONCLUSIONS

The original goals of this project were achieved with success, addressing the main drawbacks of the current commercial processes for the production of DMF:

- (a) It was possible to exclude the use of mineral acids as a catalyst, avoiding the formation of carcinogenic impurities, such as dimethyl sulfate;
- (b) The FA suspension was efficiently fed to the flow equipment, without the need of specific process stages to partially convert FA to MMF;
- (c) Optimal solvent composition was found to drive the reaction to completion and to avoid catalyst deactivation, strongly improving process efficiency;
- (d) The reaction conditions were optimized by means of DoE, to obtain high conversion with the best compromise between residence time, reaction temperature, and amount of catalyst.

The final process resulted to be sustainable, both from the economical and from the environmental point of view.

The incidence of the heterogeneous catalyst cost on the API production costs is clearly mitigated by the fact that additional downstream purification, used in prior art processes to remove critical impurities, can be avoided in this case. Besides the positive effect on global process yield, this aspect has a positive effect also from the point of view of the lower amount of wastes generated by each purification.

Moreover, this process excludes the use of water during the workup and isolation phases. For this reason, in principle, recycling of the distillates and mother liquors could be possible, with positive effects on process sustainability.

EXPERIMENTAL DETAILS

General. Solvents and reagents were obtained from commercial sources and used without purification, unless otherwise indicated.

High-purity authentic samples of all relevant materials (FA, MMF, and DMF) were purchased from trusted chemical suppliers. The identity of the species was confirmed by MS and by comparison of the retention times in HPLC.

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SiliaBond SCX-2 was purchased from SiliCycle.

HPLC analyses on all batches were carried out using the same method. Table S2 reports the details of the HPLC method.

Feed as Solution: Experimental Configuration. The system was composed of an Asia solid-phase reactor, with glass and poly(tetrafluoroethylene) (PTFE) as wetted materials (length, 100.0 mm; ID, 15.0 mm; adjustable end). The pumping unit was one Asia syringe pump. The system pressure was maintained using an Asia pressure controller. All other plumbing of reactor lines were PFA tubing (1.6 mm OD, 0.5 mm ID).

Feed as Suspension: Experimental Configuration. The system was composed of one custom-made coil (for FA dissolution), prepared with PFA tubing (3.2 mm OD, 1.5 mm ID) with a total volume of 2.0 mL, submerged in a housing filled with mineral oil at 125 °C. The coil was connected to an Asia solid-phase reactor, with glass and PTFE as wetted materials (length, 100.0 mm; ID, 15.0 mm; adjustable end). The pumping unit was a Vapourtec SF-10 laboratory pump. The system pressure was maintained using an Asia pressure controller. All other plumbing of the reactor were PFA tubing (OD, 1.6 mm; ID, 0.5 mm).

Procedures. Central Composite Design Experiments. A mixture of 120.0 g (1.03 mol) of FA and 36.0 g of Si propylsulfonic acid (SCX-2) (loading 0.67 meq/g) in MeOH (600 mL) was stirred at reflux for 1 h. After partial conversion to MMF and DMF, the catalyst was removed by filtration and DMC (1800 mL) was added. For each experiment, 100 mL of resulting solution, was pumped by a syringe pump into a glass cartridge reactor (total reactor volume, 11.0 mL; ID, 15.0 mm; see the Feed as Solution Experimental Configuration section) filled with 7.2 g of a heterogeneous catalyst (1:1, 3:1, 1:0 mixture of Si propylsulfonic acid SCX-2/Silica GE60). The reactions were run at 110, 120, and 130 °C, using residence times of 10, 20, and 30 min (see Table S1 for a detailed list of the experiments). The product, a transparent, colorless solution, was collected at the reactor outlet, after passing through the back pressure regulator set at 7 bar. The conversion of the reaction was determined by HPLC.

Catalyst Stability Test. A stirred suspension of 200.0 g (1.7 mol) of FA in MeOH (1000 mL) and DMC (3000 mL) was pumped using a Vapourtec SF-10 laboratory pump into a PFA tube reactor (total reactor volume: 2.0 mL; ID: 1.5 mm; see the Experimental Configuration section) submerged in a housing filled with mineral oil at 125 °C; in this phase, FA is completely dissolved. The solution is then directly passed to a glass cartridge reactor (total reactor volume: 11.0 mL; ID: 15.0 mm; see the Feed as Suspension Experimental Configuration section) filled with 7.2 g of heterogeneous catalyst (63:37 mixture of Si propylsulfonic acid SCX-2/Silica GE60). The pump flow rate was set at 0.37 mL/min, resulting in a residence time of 5.4 min inside the PFA reactor coil and of 30.0 min inside the glass cartridge reactor. The reaction was conducted at 125 °C. The product, a transparent, colorless solution, was collected at the reactor outlet, after passing through the back pressure regulator set at 7 bar. The conversion of the reaction is determined by HPLC.

Crude DMF Isolation. The solution obtained from catalyst stability test was concentrated to a volume of 300 mL under vacuum, and MeOH (1200 mL) was added. The resulting slurry was heated at 60 °C and then cooled at 5/10 °C. The crystalline solid was collected by filtration and washed with a mixture 8:2 of MeOH/DMC (500 mL). The product was dried under vacuum

to afford dimethyl fumarate (206.1 g, >99.5% purity by HPLC) in 83% yield.

Scale-Up Trials. In this setup, the configuration is the one described in the previous section, with a flow rate of 21.6 mL/ min, a custom-made stainless steel tube reactor of 150 mL (internal diameter, 0.2 cm), and a custom-made stainless steel cartridge reactor of 700 mL (internal diameter, 4.0 cm). The system was operated for 80 h, sampling at regular time intervals. The analytical results confirmed that observed at laboratory scale.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00503.

Data and plots from DOE experiments (Table S1 and Figures S1 and S2); SEM images for fresh and used catalysts (Figure S3); and details of the HPLC method (Table S2) (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

API, active pharmaceutical ingredient; HPLC, high-performance liquid chromatography; DMF, dimethyl fumarate; MMF, monomethyl fumarate; FA, fumaric acid; DMC, dimethylcarbonate; MeOH, methanol; CF, continuous flow; CCD, central composite design; DoE, design of experiment; SCX-2, siliabond propylsulfonic acid; SCX, siliabond tosic acid

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