Artículo Original

Síntesis a gran escala de 5-etoxycarbonil-6-metil-4-(2-nitro-fenil)-3,4-dihidro-2(1H)piridona

Large scale synthesis of 5-ethoxycarbonyl-6-methyl-4-(2-nitro-phenyl)-3,4-dihydro-2(1H)pyridone

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Resumen

El escalado de un proceso químico de obtención de una nueva entidad química, desde el laboratorio hasta la escala piloto o comercial, suele ser un proceso complejo. Está influenciado por varios parámetros, tales como: temperatura, velocidad de agitación y sus interacciones. La temperatura y la velocidad de agitación están estrechamente relacionadas con las transferencias de calor y movimiento; dos operaciones unitarias críticas que influyen en el proceso. Además, el orden secuencial de adición de reactivos podría ser uno de los fallos del escalado. Nuestro proyecto consiste en una reacción multicomponente con cuatro miembros (4-MCR) para la obtención de un derivado de 3,4-piridona (Figura 1), producto muy importante para la obtención de un novedoso compuesto neuroprotector que se encuentra en desarrollo. Por lo tanto, este estudio se centra en desarrollar una forma práctica de escalar una reacción multicomponente con 4 miembros, desde la escala de laboratorio hasta la escala piloto, aplicando una combinación del método de fuerza bruta y números adimensionales en función de las fuerzas físicas significativas que lo gobiernan. Resultados experimentales previos (Mondelo Rodríguez et al., 2017) demostraron que la temperatura y la agitación del fluido y su interacción son los parámetros más importantes que afectan el rendimiento de la reacción. Para calcular la velocidad de agitación de la escala superior se utilizaron los números de Nusselt y Reynold, además de otros criterios aplicados. Asimismo, a medida que el producto de reacción precipitó durante el proceso de enfriamiento, se determinó una velocidad de agitación crítica aplicando la regla de Zwietering. El proceso mostró una alta reproducibilidad en todas las escalas, alcanzando buenos rendimientos del 70 al 75 % y una alta pureza del producto superior al 99 % para todos los lotes. El método aplicado permite la escalabilidad exitosa del proceso para aumentar la escala a comercial.

Palabras clave: escalado, síntesis orgánica, método de la fuerza bruta, números adimensionales, Regla de Zwietering, fuerzas físicas.

Abstract

Chemical process scale-up, from laboratory to pilot or commercial scale, of a new chemical entity is commonly a complex process. It is influenced by several parameters, such as:

temperature, agitation speed and its interactions. Temperature and agitation speed are closed related to the heat and movement transfers; two critical unit operations that affect the scale-up process. In addition, the sequential order of reagent addition could be one of the scale-up failures. Our project involves a multicomponent reaction with four members (4-MCR) for obtaining a 3,4-piridone derivative (Figure 1), a very important product for obtaining a novel neuroprotective compound which is in development. Thus, this study is focused to develop a practical way for scaling-up a multicomponent reaction with 4 components, from laboratory scale to pilot scale applying a combination of the brute force method and dimensionless numbers for scaling-up the process based on the significant physical forces governing it. Previous experimental results, Mondelo Rodríguez et al. (2017) demonstrated that the temperature and fluid agitation and its interaction are the most significant parameters affecting reaction yield. The Nusselt and Reynold numbers, in addition to other criteria applied, was used for calculating the agitation speed for the upper scale. Likewise, as the reaction product precipitated through the cooling process a critical agitation speed was determined applying Zwietering rule. The process showed high reproducibility at all scales, reaching good yields 70 – 75 % and high product purity upper than 99 % for all batches. The method applied allows the successful scalability of the process for increasing the scale to commercial.
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Keywords: scale-up, organic synthesis, brute force method, dimensionless numbers, Zwietering rule, physical forces.

1. Introducción

1.1 Multicomponent reactions (MCRs).

The syntheses of organic compounds have reached a high level of sophistication and excellence; which it permits to synthetize a structurally complex compound. In chemical synthesis processes, not only seeks to generate an efficiently new bonds formation but else it is desirable a regio- and chemo-selective control too, as well as, a stereo-chemical control and reducing as possible the stage number of the process [1]. Multicomponent reactions (MCRs) comply with all these criteria and play an innovative role [2]. These reactions incorporate all starting materials (three or more) in the product structure in just one stage, where basically all or most of the atoms contribute to the newly formed product [3,4,5]. MCRs provide a new approach to the efficiently synthesis of diverse compounds and the generation of a library of compounds. Likewise, MCRs are considered as one of the more efficient strategy for synthesizing complex organic small-molecules and peptides [3,4,5,6,7].

Particularly, asymmetric multicomponent reactions (AMCRs) involve the obtaining of chiral compounds through the reaction of three or more reagents simultaneously added [1]. This kind of strategy shows some advantages over the classic one, as: cost, time and energy saving, as well as, low environmental assessment (impact) and drastically reduces effort [1,3,5]. All these advantages, in addition to the high level of stereoselectivity achieved in some reactions, have led chemists to adopt this new synthetic strategy or at least to consider it as a viable option.

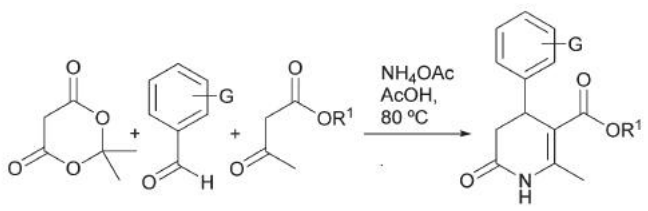

Figure 1. MCR for the synthesis of 3,4 piridones derivatives.

All multicomponent reactions (MCRs), including AMCRs, occupy a privileged position in organic synthesis and are currently gaining momentum in areas where rapid access to high levels of structural diversity is required. The majority of work has been devoted to the synthesis of heterocyclic adducts from non-heterocyclic reactants. This is especially important in medicinal chemistry and key to drug discovery. Merging the synthetic power of MCRs with the particular reactivity of heterocyclic compounds leads to an impressive array of new transformations and unprecedented connectivity patterns. These new scaffolds are produced in a straightforward manner, often by simply mixing the reactants and, due to their combinatorial nature, are amenable to parallelization. Furthermore, the highlighted processes show high levels of structural variability [3].

1.2 Scale-up

The scale-up of a chemical reaction involve several factors to be consider, which change from a reaction to another [8]. For adopting a rational and successful approach it is essential a systematic search of relevant and critical information and its understanding. The fact is that from the numerous influential factors in the reaction, only a relatively small number of it will control and determine the scale-up behavior. The focus of the activities must be identifying the key parameters of scale-up and gaining in its understanding [9]. Successful scale-up means that larger scale operations are fully anticipated and understood. Usually, the performance will be poorer than witnessed on a smaller scale. Scale-up must address several interdependent, flow-sensitive physical processes occurring simultaneously [10]. When considering laboratory reactor scale-up, the first step is to decide the directional mode of the scale-up. There are three main possibilities for reactor scaling-up:

1. Scaling up from a laboratory batch reactor to a pilot plant or commercial batch reactor.

2. Scaling up from a laboratory batch reactor to a pilot plant or commercial Continuous Stirred Tank Reactor (CSTR).

3. Scaling up from a continuous laboratory plug flow reactor to a continuous pilot plant or a continuous commercial reactor, wherein both are operating in the plug flow mode (PFA).

However, there may be other possibilities. Nevertheless, these are the most likely and most frequently encountered. In considering reactor scale-up, there are three main subjects that must be considered, which are reactor mode, mixing, and heat transfer. The need to consider these areas is not always required for each of the aforementioned cases [11]. There are four major proven scale-up methods for individual process equipment nowadays used in industry: Brute force, Model-based, Empirical and Empirical-model hybrid. Other scale-up methods applied are dimensionless numbers and direct method [12,13,14].

The brute force method is based in a scale-down version of the commercial scale design in such a way that all critical factors and conditions for scale-up are kept the same. The model-based scale-up is focused in numerical models for predicting the unit operation performance. The models contain all physical, chemical, thermo-dynamical, and hydrodynamic effects for the performance. A key factor in this method is the validation of the models by means of experimental data. The empirical scale-up method is based in the experimentation at several scales, often 3 or 4 scales. In addition to being costly and time-consuming, this method is not very reliable, as the underlying phenomena causing the scale effects are unknown and remain unknown. Also, the real critical scale-up parameters are unknown. The dimensionless numbers scale-up method, firstly, must define all dimensionless numbers from a dimension analysis of all critical parameters, and second, the values of the dimensionless numbers are kept the same at scale-up from the test unit to the commercial scale [12,13,14]. Direct scale-up means directly design, construct, and start-up a novel commercial scale process without prior research and development work. This method is sometimes used by start-up companies for processes containing one major piece of equipment. Through this approach, design capacity and the product quality could never be reached, neither with additional investment

for solving unexpecting problems. The possibility that the process will be a total failure is considerably [15]. Then, for complex projects, this is a prohibited method [13].

The 5-ethoxycarbonyl-6-methyl-4-(2-nitro-phenyl)-3,4-dihydro-2(1H)pyridone is an small molecule with a stereogenic center; which is obtained through an asymmetric 4-MCR synthesis [16,17]. This compound is the first intermediary product in the synthetic route of a new benzodiazepine API, a potential neuroprotective compound; which it is under pharmacological research [19,20,21]. That´s why, the pilot scale-up will allow to perform the required batch productions to release enough quantity of the API to carry out all regulatory preclinical assays, API and Finished Product stability studies and clinical trial for two high incidence diseases: Parkinson disease and cognitive impairment and Alzheimer

2. Materials and Methods

2.1 Materials and equipment

Common Pyrex, Quickfit and Pobel glassware and a 500 milliliters glass jacketed cylindrical reactor were used for all laboratory scale experiments. For bench and pilot scale were used a 500 mL and a 2- liters glass jacketed cylindrical reactor with an anchor agitator at both scales and similar impeller diameter to reactor diameter (d/D) for keeping geometrical similarity. Other equipment used were an overhead agitator WITEG HS100D, a Pobel magnetic stirrer with heating plate, Edward 3 vacuum pump, MLW thermostat, VWR Scientific 1162 Poly Science chiller, Sartorius analytical balance, Shimadzu UX620H semi-analytical balance, HPLC – conventional AZURA Knauer Technology with autosampler and a Salvis vacuum oven. Chemical reagents and solvents were supplied by Sigma-Aldrich and Merck. Distilled water obtained at CIDEM with Pobel DESATANK 8 distillatory.

2.2 Synthesis of 5-ethoxycarbonyl-6-methyl-4-(2-nitro-phenyl)-3,4-dihydro-2(1H)pyridone at laboratory scale

To a 500 mL glass jacketed cylindrical reactor with a reflux condenser were added 122 mL of acetic acid and it was connected the stirrer. Equimolar amount of Meldrum acid, 2-nitrobenzaldehyde and ethyl acetoacetate and 1.2 equivalent of ammonium acetate were added to the reactor. The reaction mixture was heated and refluxed for 7 hours and the reaction progress were followed through TLC, 20 x 20 cm Merck silicagel TLC plate 60G F_{254} over aluminum plate with n-hexane/ethyl acetate (1/1) and revealed under UV SPECTROLINE® ENF-240C/F lamp operating at 254 nm. After this time, the resulting mixture was cooled at room temperature. Once the temperature reaches 30 °C, 200 mL of di-ethyl ether were added and the system was kept under stirring for 30 min. The reaction mixture was discharged and filtered at vacuum. The retained solid was washed three times with di-ethyl-ether [16, 22]. The product was dried under vacuum (26,7 kPa) at 60 °C for 4 h [22].

2.3 Determination of operating conditions for bench and pilot scale

Scale-up experimentation was defined for a scale-up factor of 5, regarding to mols of the limiting starting reagent Meldrum acid, corresponding to, 100 mmols at laboratory scale, 500 mmols at bench scale and 2500 mmols at pilot scale. For bench and pilot scale operating conditions was keeping the best values of the most significant parameters obtained at laboratory scale in previous work [22]. The scale up criteria applied for estimating the stirring speed was correlated to the heat and momentum transport unit operation. Likewise, it was selected the Froude number and Zwietering criteria [24,26], due to the vortex's formation by the lack of baffles and the evidence of solid precipitation. These two additional criteria were used for determining the critical value of

agitation speed for avoiding the spill of the reaction mixture and keeping 100 % of solids in suspension, respectively.

Equal Nusselt number at both scales:

$$\frac{Nu_2}{Nu_1} = \left(\frac{(D_2{}^2 * N_2)^{2/3}}{(D_1{}^2 * N_1)^{2/3}}\right)\left(\frac{\mu b}{\mu w}\right)^{-0.03} = 1 \quad (1)$$

Equal heat transfer coefficient at both scales:

$$\frac{h_2}{h_1} = \left(\frac{(D_2{}^2 * N_2)^{2/3}}{(D_1{}^2 * N_1)^{2/3}}\right) * \frac{D_1}{D_2} * \left(\frac{\mu b}{\mu w}\right)^{-0.03} = 1 \quad (2)$$

Where h: Heat-transfer coefficient; N: stirring speed; D: inside diameter of the vessel; d: impeller diameter; ρ: density; μ: viscosity; Cp: heat capacity at constant p; k: thermal conductivity of the fluid; $\frac{\mu b}{\mu w}$: bulk-to-wall viscosity ratio [23].

Equal power per volume unit at both scales:

$$\frac{\left(\frac{P}{V}\right)_2}{\left(\frac{P}{V}\right)_1} = \frac{N_2{}^3 * D_2{}^2}{N_1{}^3 * D_1{}^2} = 1 \quad (3)$$

Where P is power; V: volume; N: stirring speed; d: impeller diameter [23,24].

Equal Reynold number at both scales:

$$\frac{Re_2}{Re_1} = \frac{N_2 \times D_2{}^2}{N_1 \times D_1{}^2} = 1 \quad (4)$$

Where N: stirring speed (min^{-1}); d: impeller diameter; ρ: density; μ: viscosity [23,24,25].

Equal tip speed at both scales:

$$\frac{v_2}{v_1} = \frac{N_2 * D_2}{N_1 * D_1} = 1 \quad (5)$$

Where v: Impeller tip speed; N: stirring speed (min^{-1}); d: impeller diameter; π: constant [23].

Equal Froude number at both scales:

$$\frac{Fr_2}{Fr_1} = \frac{N_2{}^2 * D_2}{N_1{}^2 * D_1} = 1 \quad (6)$$

Where N: stirring speed; d: impeller diameter; g: gravitational acceleration [23].

Equal Zwietering rule at both scales:

$$\frac{N_{JS2} * D_2{}^{0.85}}{N_{JS1} * D_1{}^{0.85}} = 1 \quad (7)$$

Where N_{JS}: stirring speed for just suspension; d: impeller diameter [24,26]

2.4 Reproducibility studies

The process was validated through the reproducibility of the reaction yields at all scales. The reaction process was replicated eighteen times at each scale applying the conditions reported in previous work for the better yields [22]. The result data was analyzed through the statistical software Statgraphic Centurion version 16.1.03. The means and standard deviations were determined.

2.5 Determination of agitation speed just for suspension

Five screening experiments were performed at bench scale, changing the agitation speed between 300 - 500 min^{-1} increasing it 50 min^{-1} each time. The reaction mixture was checked every 15 minutes by direct observation to determine the stirring speed at which 100% of the solids remained suspended.

3. Results and Discussion

3.1 System Classification

The reaction system is completely homogeneous while the mixture is refluxing. Once it is cooling, the product precipitates becoming in a heterogeneous mixture and the sedimentation of solids is observed. From this result, it was selected an anchor impeller for providing tangential flow that drags solids from wall and bottom of the reactor. In addition, it was necessary higher agitation speeds for keeping them in suspension. Thus, it was selected a direct observation method, at laboratory scale, changing the agitation speed from 300 min^{-1} to 500 min^{-1}, for determining the critical speed value at which solids sediment.

3.2 Synthetic pathway scale-up analysis

Although the idea of a scale-up error, associated with an incorrect theoretical approach, may seem unlikely, it can easily happen. It usually occurs because observations in bench-scale experiments that seem unusual are explained by an incorrect hypothesis. Successful implementation means that the commercial scale process meets the design targets within the planned start-up time. The purpose of industrial process scale-up is then mainly risk reduction needed for success [13,15].

Once demonstrated in previous work, the temperature and agitation speed were the more significant parameters governing the reaction process [22]. Thus, heat transfer and momentum transport were identified as the critical unit operations for the process scale-up, according to the brute force method [12,13]. From here, it was selected the Nusselt, Reynold, power per unit of volume and tip speed dimensionless numbers (Equations 1 to 4), for complying with the critical physical forces for increasing scale. For the scale-up, each selected criteria was kept equal at both scales affording the Equations 1 to 7. The reaction mixture doesn´t change with the scale change; thus, physical parameters such as viscosity, density or heat capacity at constant pressure keep constant and it can be removed from the equations. In addition, it was observed, at the cooling stage, the sedimentation of the precipitated product. Thus, it was necessary the determination of the critical agitation speed for keeping solids in suspension applying the Zwietering rule (Equation 7), as an restriction scale-up criteria, for avoiding the reactor discharges obstruction. Besides, a lot of solid keep in the vessel and it is needed large volumes of solvent for discharging it. Likewise, there was observed a strong vortices formation, due to the lack of baffles, and it was necessary to introduce the Froude number (Equation 6) for estimating the top critical agitation speed for preventing the spill of the reaction mixture. The geometric similarity was fulfilled using glass jacketed cylindrical reactors of 500 mL for laboratory and bench scale and 2000 mL for pilot scales. The reaction mixtures, at each scale, were the same, thus, the physical properties were fulfilled too.

3.3 Chemical reaction scale-up

Experiments were performed setting the conditions at which were reached the better yields in previous optimization study [22]. Bench and pilot scale were conducted at 410 min^{-1} as it was estimated through the selected scale-up criteria. The process was replicated eighteen times at each

scale, showing a high reproducibility regarding to the reaction yield and purity in all scale studied (Table 1).

The comparative ANOVA analysis of the yields at all scales (Table 2) showed a P-value higher than 0,05; thus, there is no statistically significant difference between the means of the three scales with a 95.0% confidence level; demonstrating the reproducibility of the results. This result suggests that the applied reaction conditions could be successfully used at higher scales, including to the commercialization scale. Laboratory and bench scale were performed in the same 500 mL glass reactor, because of this reaction vessel admit the nominal volume of the reaction for both scales. Pilot scale was performed at the 2000 mL reactor.

Table 1. Yield and purity of the product at each scale.

	Lab. Scale		Bench Scale		Pilot Scale	
Exp. No.	Yield (%)	Purity (%)	Yield (%)	Purity (%)	Yield (%)	Purity (%)
1	72,5	99,4	73	99,6	71	99,5
2	70	99,4	70	99,4	70	99,6
3	72	99,6	74	99,5	72	99,7
4	76	99,3	71	99,5	74	99,5
5	75	99,8	73	99,7	75	99,5
6	72,2	99,9	73	99,6	74	99,4
7	73	99,5	75	99,5	73	99,6
8	75	99,6	72	99,6	75	99,5
9	70	99,7	71	99,7	70	99,6
10	76	99,5	70	99,5	72	99,7
11	76	99,5	74	99,5	72	99,5
12	72	99,4	76	99,4	76	99,4
13	71	99,3	73	99,6	75	99,5
14	74	99,6	75	99,5	71	99,5
15	74	99,5	70	99,6	70	99,4
16	70	99,6	75	99,7	75	99,6
17	73	99,7	76	99,5	76	99,5
18	75	99,5	76	99,4	75	99,6
average	73,15	99,54	73,17	99,54	73,11	99,53
sd	2,034	0,157	2,061	0,095	2,079	0,088

Fig. 2. Reverse phase HPLC chromatogram of 5-ethoxycarbonyl-6-methyl-4-(2-nitro-phenyl)-3,4-dihydro-2(1H)pyridine, batch 23006-I (source: Mondelo et al. 2017)

Table 2. ANOVA.

Source	*Sum of Squares*	*DF*	*Medium Square*	*F-ratio*	*P-value*
Between groups	5,8086	2	2,9043	0,68	0,5122
Intra groups	253,241	59	4,29222		
Total (Corr.)	259,05	61			

Reaction yield data at each scale fits normal probability distribution. The density function shows an almost overlapping Gaussian bell for bench and pilot scale data set (Figure 2) evidencing a higher reproducibility in its results.

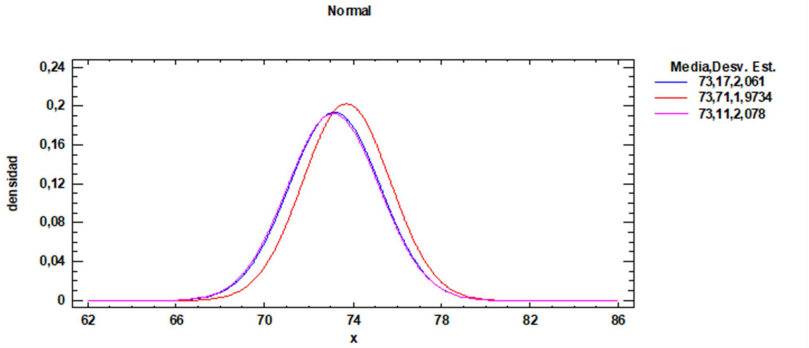

Fig. 3. Density function of the yield data set for each scale.

3.4 Stirring speed estimation

The stirring speed at upper scale (bench or Pilot) was cleared from each scale-up criteria applied (Equations 1-7). In Table 3 is reported all calculated values of the agitation speed by all criteria considered. Screening experiments, at bench scale, changing the agitation speed between 300 - 500 min^{-1} afford the exact value of this parameter for keeping the 100 % of solid suspended and avoiding solids sedimentation in the reactor. This value was applied in the Zwietering criteria (Equation 7) for determining the speed for just suspension at pilot scales. The critical values of 419 min^{-1}, calculated through Froude number, and 399 min^{-1}, calculated by Zwietering criteria, established the agitation speed higher and lower limits for a safety operation. Nevertheless, none analyzed criteria report a speed value between those limits, thus the experimental agitation speed was selected empirically. In addition to the scale-up criteria defined, the heat transfer coefficient scale-up criteria were considered by clearing it from the Nusselt number (Equation 2); reporting 472 min^{-1}, excessively high related to the upper limit speed defined (Table 3).

Table 3. Stirring speed calculated by different scale-up criteria.

No.	Criteria	$N_{calculated}$ (min^{-1})
1	$Nu_1 = Nu_2$	230
2	$h_1 = h_2$	472
3	$Re_1 = Re_2$	143
4	$Fr_1 = Fr_2$	419
5	$v_1 = v_2$	293
6	$(P/V)_1 = (P/V)_2$	372
7	Zwietering rule	399

The value obtained for Reynold number criteria is very low, considerably lesser than the half of the critical lower limit of 399 min^{-1}, established by Zwietering rule. Nevertheless, as Reynold number is included in the Nusselt number equation, this is already considered for scaling-up (Equation 1). Experimentally, the stirring speed selected was 410 min^{-1}, corresponding with the average speed between both constraint limits. Although stirring speed selected is relatively low respect to the value calculated by the heat transfer coefficient criteria, reaction scale-up was successfully performed. Reaction yields was very similar in all scale evaluated. Table 4 report the average reaction yield at each scale with the standard deviation. The process was replicated eighteen times; showing high reaction yields and a good reproducibility when increasing scales (Tables 1 and 4). Besides, the product purity was checked by HPLC showing a very high purity directly from the synthesis, upper than 99 % (see Figure 2).

Table 4. Experimental reaction yield at each scale.

Scale	Starting mols of Meldrum acid	Yield (%)
Laboratory	0.1	73,71 ± 1,9734
Bench	0.5	73,17 ± 2,0615
Pilot	2.5	73,11 ± 2,0787

3.5 Discussion

Process scale-up was successfully accomplished through the integration of brute force method and dimensionless number method. The study at bench scale permitted to evaluate the better reaction parameters obtained in previous work at laboratory scale [22]. The reaction yield was very similar in all reaction scale (Table 4). The process reproducibility was reached at laboratory and bench scale in a 500 mL glass jacketed reactor, and at pilot scale in a 2000 mL glass jacketed reactor. In addition, a technological improving was performed by introducing a purification step by adding di-ethyl ether to the reaction mixture once 30 °C were reached inside the reactor. In addition, another 30 min of agitation were added for permitting the di-ethyl ether to extract impurities. This additional step conduces to obtain a product with high purity, determined by HPLC with diode array detector (Figure 1), after filtration and consecutive washing with di-ethyl ether. Likewise, first experiments at bench scale showed sedimentation of the product during the cooling process at relative lower agitation speeds and the obstruction of the reactor discharge. This behavior wasn´t be seeing at laboratory scale due to the lower reaction volume. Thus, the agitation speed that keep suspended all solid was experimentally determined by direct observation over a wide range agitation speed, from 300 - 500 min^{-1}. This agitation speed value become in a critical parameter for scaling-up: agitation speed just for suspension and it was included as a critical scale-up criterion for a successful process, through the Zwietering rule (Equation 7).

The agitation speed calculated when applied the heat transfer coefficient scale-up criteria (Equation 2) showed the higher value of 472 min^{-1}. Nevertheless, it couldn´t be evaluated because of the restriction value introduced by Froude number criteria for avoiding reaction mixture spill from the reactor. Another lower agitation values doesn´t be studied due to the lower agitation speed restriction established by the Zwietering criteria. The agitation speed of 410 min^{-1} was selected based over the average value for moving off the limit restriction values. The experimentation at pilot scale was replicated several times showing a high reproducibility with a low standard

deviation (Table 2); demonstrating a successful process. This reproducibility was evidenced too in the purity of the product upper than 99 % without additional complex purification processes.

4. Conclusions

The reaction process was successfully scaled-up to pilot scale applying the brute force method combined with the dimensionless number method. The process at each scale was replicated 18 times evidencing the reproducibility of the process. High product purity was reached directly from the synthesis, at each batch, without any complex purification process (Table 1). The scale-up process afforded enough amount of the product for continuing the technologic and clinical development of a new neuroprotective API.

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Conflicts of Interest

The authors declare no conflicts of interest.

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