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Extruder scale-up assessment in the process of extrusion–spheronization: comparison of radial and axial systems by a design of experiments approach

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Abstract

Scaling-up the extrusion–spheronization process involves the separate scale-up of each of the five process steps: dry mixing, granulation, extrusion, spheronization, and drying. The aim of the study was to compare two screw extrusion systems regarding their suitability for scaling-up. Two drug substances of high- and low-solubility in water were retained at different concentrations as formulation variables. Different spheronization times were tested. The productivity of the process was followed up using the extrusion rate and yield. Pellets were characterized by their size and shape, and by their structural and mechanical properties. A response surface design of experiments was built to evaluate the influence of the different variables and their interactions on each response, and to select the type of extrusion which provides the best results in terms of product quality, the one which shows less influence on the product after scale-up ("scalability") and when the formula used changes ("robustness"), and the one which allows the possibility to adjust pellet properties with spheronization variables ("flexibility"). Axial system showed the best characteristics in terms of product quality at lab and industrial scales, the best robustness at industrial scale, and the best scalability, by comparison with radial system. Axial system thus appeared as the easiest scaled-up system. Compared to lab scale, the conclusions observed at industrial scale were the same in terms of product quality, but different for robustness and flexibility, which confirmed the importance to test the systems at industrial scale before acquiring the equipment.

Keywords: Extrusion–spheronization, scale-up, response surface, screw extruder, industrial scale, robustness, flexibility

Introduction

Scale-up, which predicts the transition from lab batch to pilot and then to industrial batches, is a fundamental step in the drug development. As a matter of fact, increasing batch size may lead to a change in equipment, manufacturing site or process, and it is essential to evaluate the consequences of these changes[1]. The objective, by scaling-up a lab process to industrial scale, is to check that the industrial process is feasible with or without process modifications (as minimum as possible) and reproducible, to demonstrate that the product obtained at industrial scale is identical to the one elaborated at lab scale and also to demonstrate the formulation and process robustness when the batch size increases. Critical parameters must be identified for each manufacturing scale in order to set the process limits.

Authors described different approaches for scaling-up a process to another scale: (i) monitoring of one

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representative parameter; (ii) search of scale-up dimensionless numbers that completely characterize the process to express geometric and dynamic similarities between two scales[2,3]; (iii) construction of experimental designs to establish models able to estimate the quality of the product when the process conditions are changed. The design of experiments approach is a powerful tool for optimisation and process scaling-up: it allows a rational study of experimental parameters influence on selected responses with a shorter experimentation time and an improved process comprehension[4,5]. It also provides assurance of quality after a scale-up operation by a "quality by design" approach, where all critical sources of variability are identified and explained, and where product quality can be accurately and reliably predicted over the design space established.

Among the different methods to produce pellets, the process of extrusion–spheronization is of particular interest, and is widely described in the literature[6–11]. The scale-up of the extrusion–spheronization process involves the separate scale-up of each of the five process steps: dry mixing, granulation, extrusion, spheronization, and drying. This study focuses on the extrusion step scale-up. Among the different types of extruders on the market (screw-feed, gravity feed, ram extruders), this work is limited to screw-feed extruders, which can be classified in three categories according to the design of the screen: axial, dome, and radial[8]. This study compares the scale-up of a lab mono-screw extruder and of an industrial twin-screw extruder, for radial and axial systems. Because extrusion is a continuous process, the pilot devices correspond to industrial equipments, the batch size depending on the process time.

Previous studies compared three single-screw extrusion systems (radial, dome, and axial) at lab scale to evaluate, with the help of designs of experiments, their suitability to provide good results in terms of product quality, when formulation and process parameters changed[12,13]. Few other authors studied the comparative influence of radial and axial single-screw extruders at lab scale using different formulations, on the extrusion process characteristics[14,15], and on the final product quality[14,16,17]. Only few authors carried out studies at industrial scale on twin-screw extruders for extrusion–spheronization. Most of them used radial twin-screw extruders, either for a specific extrusion study[18–20], or for a global extrusion–spheronization study[21–23]. Others used dome twin-screw extruder[24]. Axial twin-screw extruder was mentioned as being used for extrusion–spheronization in one study where the axial extruder was actually a system for wet granulation[25]. One patent detailed quite extensively the development of twin-screw extruder technology from axial extruders, through radial screen extruders, to dome extruders[26]. No author studied the screw extrusion scale-up in the process of extrusion–spheronization.

The aim of the study is to compare radial and axial screw extrusion systems for their capacity to scale-up, and to study the influence of formulation (drug substance solubility and concentration) and process variables (spheronization time) between the two scales for the two extrusion systems. The other steps are kept at lab scale in order to focus on the extrusion step scale-up. A response surface design of experiments is set up to underline the influence of the different variables and their interactions. The objective is to identify the type of extruder that suits the best for scaling, *i.e.* the one which gives the best results in terms of productivity and pellet characteristics ("product quality"), the one which shows less impact on the product after scale-up ("scalability"), the one which shows the least influence on these same properties when the formula used changes ("robustness"), and the one which allows the possibility to adjust or improve pellets properties with spheronization variables ("flexibility").

This study provides a global vision of process scale-up by using a surface response design of experiments, responding to a quality by design approach. This study analyzes the results by crossing them, introducing the notions of robustness, flexibility, and scalability.

Methods

Raw materials

Pellets were prepared from the binary mixture of a drug substance (DS) and microcrystalline cellulose (MCC). Two drug substances DS1 and DS2 supplied by Pierre Fabre Research Institute were tested, DS1 corresponding to an antidepressant, and DS2 corresponding to theophylline. The two drug substances have been chosen for their different solubility in water (1250 g/L for DS1 and 8 g/L for DS2). MCC (Avicel® PH101), supplied by FMC Biopolymer (Philadelphia, USA), is insoluble in water. Three ratios of DS/MCC were tested for both drug substances: 20:80, 36:64 and 52:48 (%w/w).

Purified water was used as liquid binder, and was adjusted for the six different formulations. The optimal water quantity required for each of the six formulations, *i.e.* the percentage of water which gives the best yield of good quality pellets (% w/w in relation to the amount of solid mass), was determined by preliminary experiments at lab scale.

Description of the experimental design

A response surface design of experiments was built with Design Expert® software, version 7.0.1.0 (Stat-Ease, Minneapolis, USA). The mathematical model targeted for each response studied was a quadratic model with first-order interactions. Five factors were studied: drug solubility in water [DS1–DS2] (g/L), drug concentration [20–36–52] (%), extrusion system [radial–axial], extruder scale [lab–pilot], and spheronization time [2–3–4] (min). To analyze the results, drug solubility, extruder system, and extruder scale were considered as qualitative factors, whereas drug concentration and spheronization time were continuous factors.

The design of experiments was built as a set of 8 designs, each corresponding to one combination of

three qualitative factors. For each of these 8 designs, a response surface was built where DS concentration and spheronization time were tested, and three replicates of the central point were run (level 0, i.e. 36% of DS and 3 min of spheronization time). The same experiments were thus repeated for both DS solubility, on the two extrusion systems, at lab and industrial scales. The whole experimental design included a total of 64 (8 × 8) experiments. Figure 1 summarizes factors and responses selected for the global design of experiments. The responses associated are described in the section "Characterizations ".

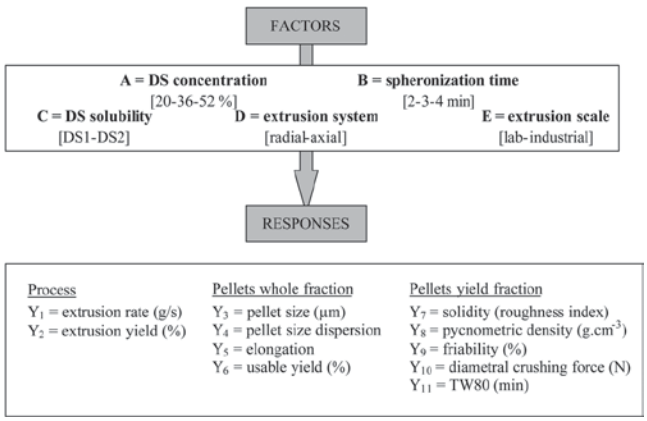

Figure 1. Experimental design: factors and responses.

Pellet preparation

Process conditions were set according to the flow chart shown in Figure 2. After dry blending of MCC and DS, wetting and granulation were performed in an Aoustin kneader (RPA Process, Nanterre, France). The water quantity was adjusted at lab scale according to the formula. The value of water quantity for which pellets could be formed was found to be dependent on the drug solubility and its concentration. The optimal water amount at lab scale was found to decrease with DS solubility and concentration increase[13]. The water quantities used at industrial scale were those optimized at lab scale.

The wet mass obtained was extruded with a lab MG-55 or an industrial EXDCS-100 extruder, both from FujiPaudal (The FitzPatrick Company Europe, Sint-Niklaas, Belgium), using the radial or the axial extrusion system. The extrudates were then spheronized in a spheronizer 250 (Caleva, Sturminster Newton, Dorset, UK) and the pellets obtained were dried in a drying oven (Heraeus, Hanau, Germany), and calibrated (Retsch GmbH, Haan, Germany) to obtain a [1400–2000] µm fraction.

MG-55 presents a single screw (160 × 55 mm), whereas EXDCS-100 presents two contra-rotatives screws (31.6 × 9.8 cm). For the extrusion step, whatever the extrusion system and scale, a screen die of 2 mm in diameter and a screw speed of 40 rpm were used to allow comparisons.

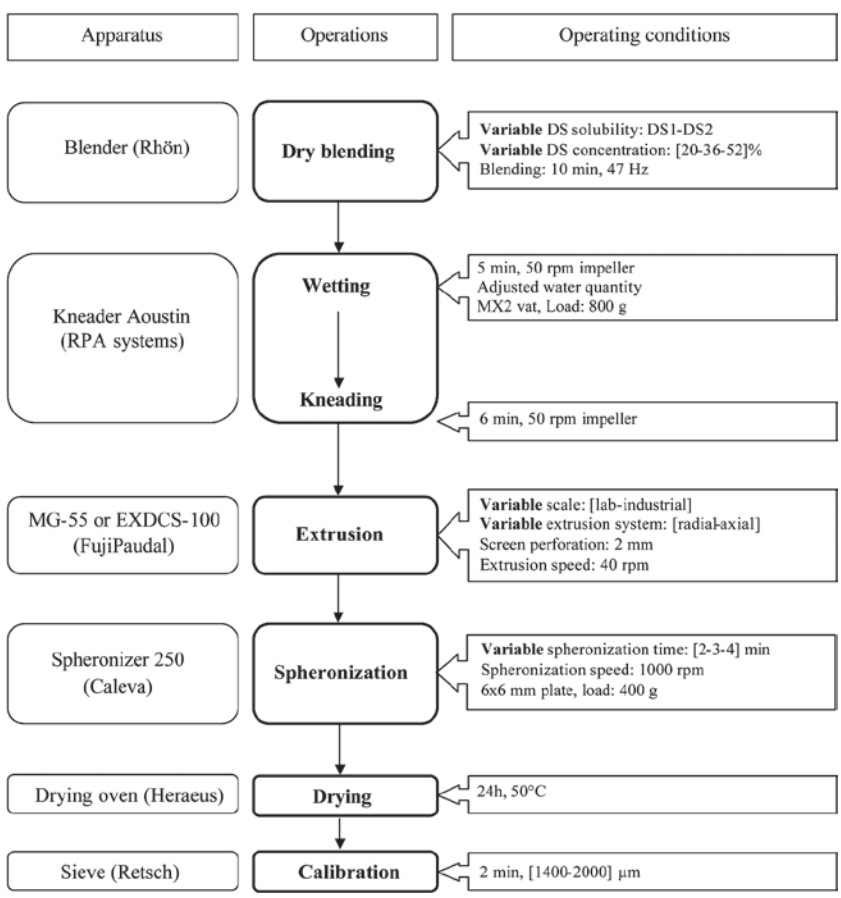

Figure 2. Pellet elaboration flow chart.

In the lab and industrial axial systems, a flat end-plate screen is placed in front of the one or two flat blades positioned to the end of the screw(s), so that the extrudates are ejected out of the screens at the end of the extruder. In the lab and industrial radial systems, two semi-cylindrical screens are placed along each side of the one or two counter rotating extruder head(s) positioned to the end of the screw(s), so that the extrudates are ejected perpendicularly to the motion of the screw(s), each head consisting of a truncated cone with three attached blades. For both scales, the extrusion screen presents a 1- and 2-mm screen thickness, respectively for radial and axial system.

Characterizations

The different responses, corresponding to the different characterizations, are reported in Figure 1.

Extrusion process

Extrusion rate and extrusion yield were studied in order to follow the productivity of each extruder system.

The extrusion rate R_E (g.s^{-1}) was calculated according to:

$$R_E\ (\text{g.s}^{-1}) = \frac{M_E\ (\text{g})}{T_E\ (\text{s})} \tag{1}$$

where M_E corresponds to the mass of wet extrudates recovered at the end of the extrusion step, and T_E to the time necessary to extrude this mass.

The extrusion yield Y_E (%) was calculated according to:

$$Y_E\ (\%) = \frac{M_E\ (\text{g})}{M_{WM}\ (\text{g})} \times 100 \tag{2}$$

where M_{WM} and M_E correspond respectively to the mass of wet powder initially introduced in the extruder and to the mass of wet extrudates at the end of extrusion.

An extrusion rate and an extrusion yield are expected as high as possible to improve the productivity of the process.

Pellet hole fraction

Size distribution Particle size distribution of the pellets was determined with a laser diffractometer (Mastersizer 2000, Malvern Instruments, Malvern, UK), equipped with a dry powder dispersing system (Scirocco 2000; Malvern Instruments, Malvern, UK), using a dispersion pressure of 1 bar, and by a microscopic method (Morphologi G2), described below. Particle size distributions were characterized by their volume median diameter ($d_{0.5}$, µm) and their pellet size dispersion (d_g).

For the design of experiments analysis, the volume median diameter D[4-3] (µm) calculated by laser diffraction was used: a sieving of 2000 µm opening was carried out before the measure, the pellet fractions over this size being then re-entered in the results. Pellet mean size must be inferior to the diameter of the extruder die diameter (2 mm) considering densification and water evaporation during the spheronization and the drying stages.

For the design of experiments analysis, the pellet size dispersion calculated by microscopy was used. The pellet size dispersion was calculated from $d_{0.5}$, $d_{0.1}$ and $d_{0.9}$, according to the following equation:

$$d_g = \frac{(d_{0.9} - d_{0.1})}{d_{0.5}} \tag{3}$$

where $d_{0.1}$ and $d_{0.9}$ values are the particle diameters corresponding to respectively 10% and 90% of the cumulative distribution. Pellet size dispersion is required to be as narrow as possible, which is expressed by a low d_g value (less than 3), to facilitate a possible later coating or capsule-filling operation.

Morphology The morphological analysis of pellets was performed by means of a particle-image analyzer (Morphologi G2; Malvern Instruments, Malvern, UK). Analysis was carried out on around 300 pellets. Pellet elongation (E) was calculated according to the following formula:

$$E = 1 - \left(\frac{\text{width}}{\text{length}}\right) \tag{4}$$

Because the pellets are possibly filled into capsules, they should present good flow characteristics and be as spherical as possible. For a perfect disk, the value of the elongation factor equals 0. It is desirable to obtain pellets with the least possible elongation.

Usable yield The pellet whole fraction was sieved on 1400–2000-µm sieves (Retsch, Haan, Germany) for 2 min, at a frequency of 60 Hz with an amplitude of 1 mm. The 1400–2000-µm fraction of pellets was considered to be the usable fraction. The authors used this fraction for pellet characterizations to eliminate the effect of size on the pellet mechanical properties. The usable yield had to be as high as possible.

Pellet usable fraction

Roughness Roughness analysis of the pellet yield fraction was assessed by measuring solidity factor using a Morphologi G2 (Malvern Instruments, Malvern, UK). Analysis was carried out on around 300 pellets from the usable yield fraction. Solidity factor (S) was calculated according to the following formula:

$$S = \frac{A}{(\text{A+B})} \tag{5}$$

in which, A is pellet area and A+B is the area enclosed by the convex hull (A+B). High solidity is desirable because it corresponds to low roughness; rough pellets may generate fines or have poor flow characteristics. Surface roughness of the pellets is also an important characteristic when considering possible coating or compression into tablets.

Pycnometric density Pycnometric density of pellets, D_{pycno} (g.cm^3), was determined using a helium

pycnometer (Accupyc 1330, Micromeritics Instrument, Norcross, USA) Samples were degassed under 6.5 Pa vacuum (VacPrep 061, Micromeritics Instrument) for 2 days at about 25°C. Measurements were performed using a 10 cm^3 cell, and repeated until the value stabilized. The mean pycnometric density was calculated from the final three stabilized data points.

Friability Friability $F(\%)$ was measured on approximately 20 g of pellets from the usable yield fraction, to which were added 40 g of 6-mm glass beads. After 30 min of blending in a 200-mL flask in a shaker–mixer (Turbula, GlenMills, Clifton, NJ, USA) at 42 rpm, the mass retained on a 1400-µm sieve was weighed, and the friability $F(\%)$ was calculated according to the following equation:

$$F(\%) = [(Mi - Mf) / Mi] \times 100 \quad (6)$$

where Mi is the mass of granules before the test (i.e. 20 g) and Mf is the mass of granules retained by the sieve after the test. The test was performed in triplicate. The friability test showed the pellet surface resistance to abrasion, which should be as high as possible to avoid abrasion during further processing.

Diametral crushing force The resistance to crushing R (N) was tested on 20 pellets of the usable yield fraction with a durometer (Computest, Kraemer Elektronik, Darmstadt, Germany). The diametral crushing force measured indicates the mechanical robustness of the pellets. It should be as high as possible to avoid pellet breakage during further processing.

Design of experiments interpretation

The mathematical model generated for each response Y was a quadratic model with first-order interactions, built according to the following equation:

$$Y = a_0 + a_i X_i + a_j X_j + a_{ij} X_i X_j + a_{ii} X_i^2 + a_{jj} X_j^2 + \varepsilon \quad (7)$$

in which X_i and X_j represent the levels of the factors; a_0 is the intercept representing the mean of the measured response data; and a_i and a_j, a_{ii} and a_{jj}, and a_{ij} correspond to the coefficients of first-order terms, the coefficients of second-order quadratic terms, and the coefficient of second-order interaction terms, respectively. The coefficient corresponding to a factor or an interaction shows its importance on the studied response. The symbol ε represents pure error. To simplify the design of experiments interpretation, the coefficients of second-order quadratic terms were not presented in this study. The coefficient values were expressed in coded units in order to compare their relative effect to that of the others. Analysis of variance (ANOVA) was performed to determine the significance of the model. A term that had a probability value lower than 0.05 was considered as significant. A probability value greater than 0.10 was regarded as not significant.

The ideal industrial extrusion system is the one which gives the best results in terms of productivity and pellet characteristics ("quality"), the one which shows less impact on the product after scale-up ("scalability"), the one which shows the least influence on these same properties when the formula used changes ("robustness"), and the one which allows the possibility to adjust or improve pellet properties with spheronization variables ("flexibility").

Results and discussion

Experiment feasibility

Pictures of extrusion step on the two extrusion systems at lab and industrial scales are presented in Figure 3. For axial extrusion, all experiments were feasible at industrial

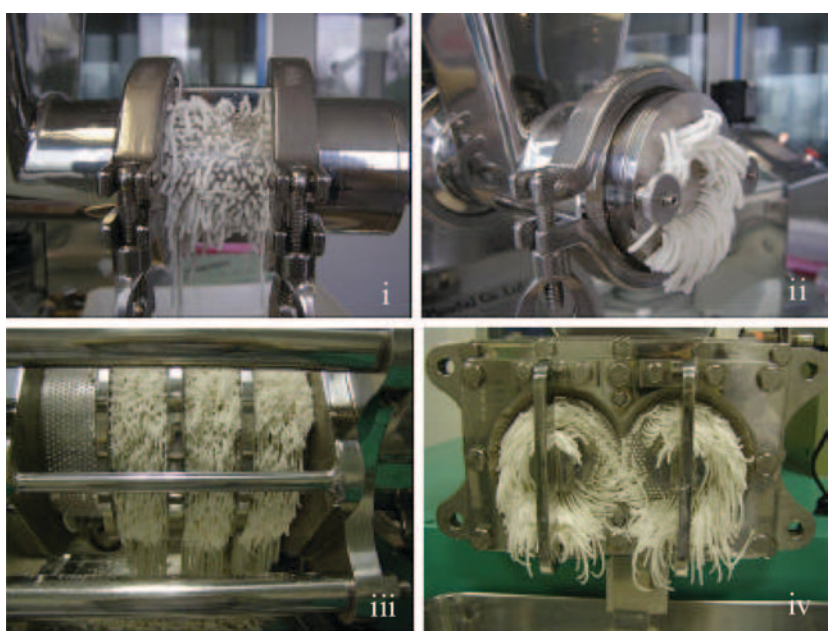

Figure 3. Extrusion of the wet mass in the MG-55 lab system: (i) radial, (ii) axial, and in the EXDCS-100 industrial system: (iii) radial, (iv) axial.

scale, using water quantities optimized at lab scale. No water readjustment was thus necessary after scale-up. For radial extrusion, using water quantities optimized at lab scale, experiments were not all feasible at industrial scale.

As a matter of fact, a dewatering phenomenon appeared for some batches at industrial scale for radial system, corresponding to the wet masses containing more than 40% of water. During the extrusion of wet mass, after a more or less short time depending on the batches, the following events appeared chronologically: (i) extrusion rate decreased, (ii) extrudates formed out were very wet, (iii) water flowed along the screen (drainage), (iv) extrusion stopped. In these cases, the extrudates recovered after the beginning of the phenomenon were not usable for the next spheronization steps.

This phenomenon can be explained by the low quantities of wet mass used in our work. The extrusion of a high quantity of product, as normally expected on an industrial extruder, should avoid the drainage phenomenon: as a matter of fact, in this case the wet mass should stay for less time in the device as pushed by the incoming product, thus decreasing the possibility of water migration.

Design of experiments interpretation

The effects of factors and main interactions between the factors, deduced from the analysis of the experimental design, are summarized with bar graphs on Figure 4. The red bars correspond to the factors that significantly influence the response Y_x.

No pellets could be formed for the batches which have shown a drainage phenomenon (4 batches): these batches were not included in the design of experiments. Nevertheless, this lack of data showed no impact on the design of experiments interpretation. The drainage phenomenon should nevertheless be kept in mind for the discussion.

Global analysis

Global analysis allowed identifying the significant factors and interactions on the different responses. It thus allowed studying the global influence of formulation and spheronization variables, and the global impact of extrusion system and scale-up, and their interactions, on productivity and pellet quality. It thus showed a global vision of the experimental design.

Formulation variables showed to have a significant impact on all the responses, excepted on pellet circularity. The influence of drug solubility and concentration on product characteristics is linked to the corresponding water quantity used, as described in a previous work[13]. Spheronization time increase showed a favourable effect on pellet morphology and mechanical properties (pellet dispersion, elongation, roughness and friability decrease) and increased pellet diameter.

The system of extrusion showed a significant impact on all the responses, except on the pellet pycnometric density. The extrusion scale showed a significant impact on all characteristics, except on pellet circularity. Moreover, in addition to the numerous interactions with formulation and spheronization variables, the design of experiments underlined interactions between extrusion system and scale for a majority of responses: this therefore requires a more detailed analysis.

The objective of the study is not to describe the influence of formulation and spheronization variables on the different responses, but to use their variations to better compare the different extruder systems at different scales. The goal is to "stress" the manufacturing process, *i.e.* to vary the various parameters identified as critical to a certain limit of change and examine the results they provide on the different systems and scales.

The ideal pilot extrusion system is the one which gives the best results in terms of productivity and pellet characteristics ("quality"), the one which shows less impact on the product after scale-up ("scalability"), the one which shows the least influence on these same properties when the formula used changes ("robustness"), and the one which allows the possibility to adjust or improve pellet properties with the spheronization variables change ("flexibility"). For this purpose, the influence of the different variables was studied by analyzing (and crossing) the results according to the scale or/and the extrusion system, by detailing the global design of experiments into several designs.

Analysis by scale ("quality" study)

Analysis by scale (lab *vs* industrial scale) allowed identifying the extrusion system giving the best results in terms of productivity and pellet characteristics at industrial scale, compared to lab scale. The two different scales were analysed separately as two distinct designs of experiments (Table 1) in order to study the influence of the extrusion system (*E*) according to the scale. Analysis by scale also allowed studying the influence of formulation and spheronization variables according to the scale.

For both lab and industrial scales, the extrusion system showed a significant influence on all responses, except on pellet pycnometric density at lab scale, and on pellet elongation, roughness and yield at industrial scale. Industrial scale thus showed a better robustness in terms of pellet morphology when the extrusion system changes, compared to lab scale.

For both lab and industrial scales, axial system showed the best characteristics in terms of productivity (except for extrusion rate at lab scale) and pellet quality. Axial system also produced pellets with higher diameter compared to radial system. These conclusions showed that in addition to the better robustness at industrial scale when extrusion system changes, the axial system identified at lab scale as the best one in terms of product quality is refunded as the best one at industrial scale.

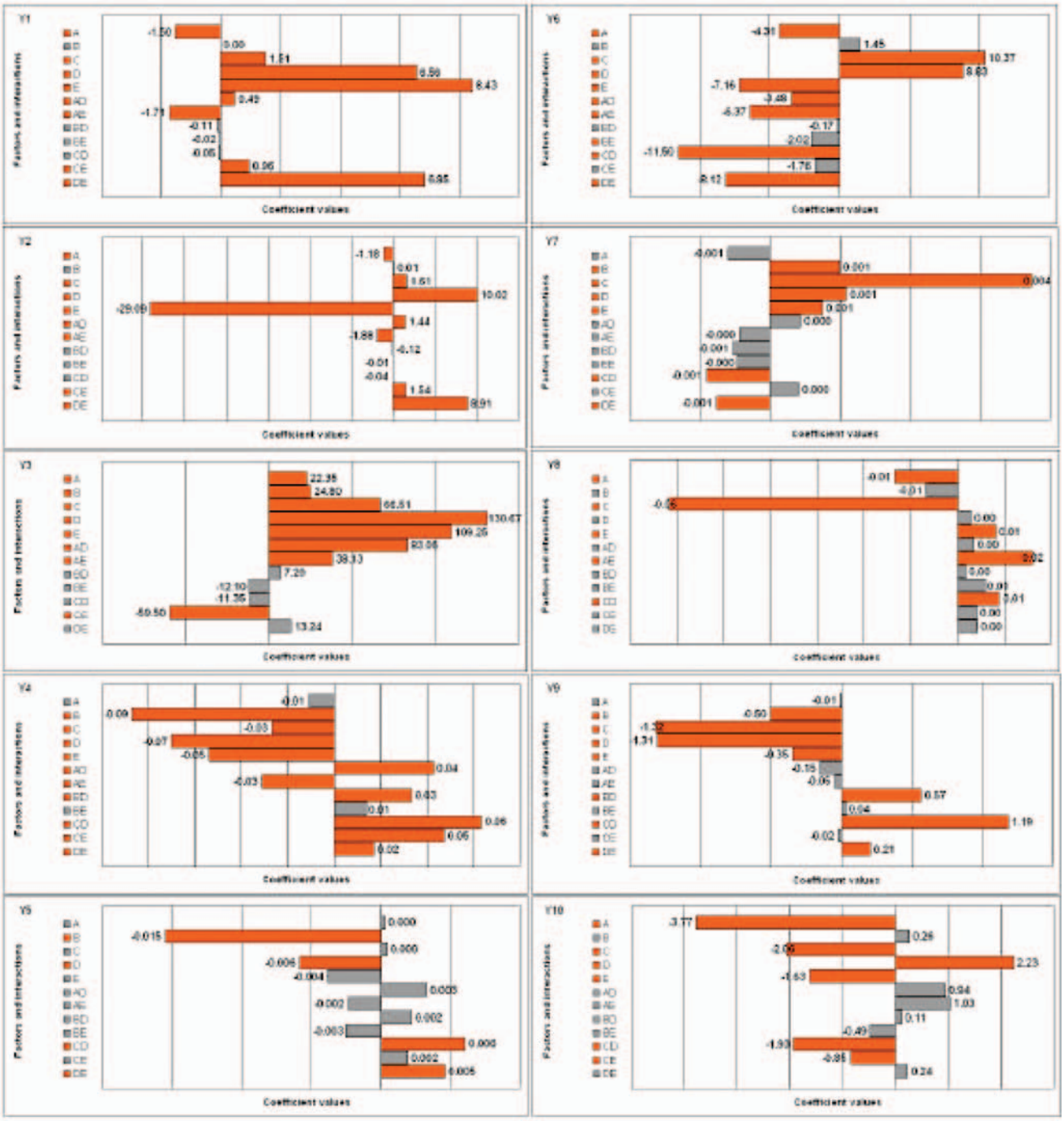

Figure 4. The effects of factors and main interactions on various responses Y_x. A = DS concentration, B = Spheronization time, C = DS solubility, D = Extrusion system, E = Extrusion scale, AD = Interaction between DS concentration and extrusion system, AE = Interaction between DS concentration and extrusion scale, BD = Interaction between spheronization time and extrusion system, BE = Interaction between spheronization time and extrusion scale, CD = Interaction between DS solubility and extrusion system, CE = Interaction between DS solubility and extrusion scale, DE = Interaction between extrusion system and extrusion scale. Y values are defined in Figure 1.

Analysis by extrusion system ("scalability" study)

Analysis by extrusion system (radial *vs* axial) allowed identifying the easiest scaled-up system, *i.e.* the one which showed less impact on product characteristics after the scale-up. The two different extruder systems were analysed separately as two distinct designs of experiments (Table 2) in order to study the significant impact of scale-up according to the extruder. Analysis by extrusion system also allowed studying the influence of formulation and spheronization variables according to the extrusion system.

For both extrusion systems, the scale-up had a favourable impact on extrusion rate, but a negative effect on extrusion yield (due to the humid mass quantities used at industrial scale similar to the extruder dead zone). For both extrusion systems, the scale-up led to a pellet size

Table 1. Detailed experimental design analysis by scale. Influence of the radial to axial system change (i.e. influence of axial system by comparison with radial system): no impact; positive impact; negative impact.

	Lab scale				Industrial scale			
Responses	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Y1	↗	NS	↗	↘	NS	NS	↗	↗
Y2	↗	NS	NS	↗	↘	NS	↗	↗
Y3	NS	↗	↗	↗	↗	NS	NS	↗
Y4	↗	↘	↘	↘	↘	↘	NS	↘
Y5	NS	↘	NS	↘	NS	↘	↗	NS
Y6	NS	NS	↗	↗	NS	NS	↗	NS
Y7	NS	↗	↗	↗	NS	↗	↗	NS
Y8	↘	↘	↘	NS	NS	NS	↘	↗
Y9	NS	NS	↘	↘	↘	NS	↘	↘
Y10	↘	NS	↘	↗	↘	NS	↘	↗

NS = no significant effect of the factor on the response.
↗ = the value of the response significantly increases with the factor (*i.e.* when the factor increases)
↘ = the value of the response significantly decreases with the factor (*i.e.* when the factor decreases).
A = DS concentration, B = Spheronization time, C = DS solubility, D = Extrusion system.
Y values are defined in Figure 1.

Table 2. Detailed experimental design analysis by extrusion system. Influence of the lab to industrial scale-up: no impact; positive impact; negative impact.

	Radial system				Axial system			
Responses	**A**	**B**	**C**	**E**	**A**	**B**	**C**	**E**
Y1	↘	NS	↗	↗	NS	NS	NS	↗
Y2	↘	NS	↗	↘	NS	NS	↗	↘
Y3	↘	↗	↗	↗	↗	↗	↗	↗
Y4	NS	↘	↘	↘	↗	↘	↗	↘
Y5	NS	↘	NS	NS	↗	↘	↗	↗
Y6	↗	NS	↗	NS	↘	NS	NS	↘
Y7	NS	↗	↗	↗	NS	NS	↗	NS
Y8	NS	NS	↘	NS	NS	NS	↘	↗
Y9	↘	NS	↘	↘	NS	NS	NS	NS
Y10	↘	NS	NS	↘	↘	NS	↘	↘

NS = no significant effect of the factor on the response.
↗ = the value of the response significantly increases with the factor (*i.e.* when the factor increases).
↘ = the value of the response significantly decreases with the factor (*i.e.* when the factor decreases).
A = DS concentration, B = Spheronization time, C = DS solubility, E = Extrusion scale.
Y values are defined in Figure 1.

increase and hardness decrease, considered as unfavourable effects, because it needs to readjust water quantity at industrial scale to produce pellets of similar size and hardness to those obtained at lab scale. The scale-up nevertheless led to an improved dispersion for both systems.

For radial system, scale-up showed no impact on pellet elongation, yield and density, and a favourable effect on pellet roughness and friability. For axial system, scale-up showed no influence on pellet roughness and friability, a favourable impact on pellet density, but a negative effect on pellet circularity and yield. Considering these results, it appears that radial system showed a little lower impact after scale-up than axial system. Moreover, these results do not take into account that several experiments could not be reproduced at industrial scale, especially with formulations containing high water quantities, causing drainage problems. Considering that, it can be concluded that axial system is the easiest scaled-up system in our work.

Analysis by scale and extrusion system ("robustness" and "flexibility" study)

Analysis by extrusion system and scale allowed to identify the kind of extruder which gave the best results in terms of process robustness and flexibility. The different extruders and scales were analysed separately as four distinct designs of experiments (Table 3) to study, for each combination, the significant effects of formulation and spheronization factors. The best system is the one which shows the less influence on the product properties when the formula used changes ("robustness"), and the one which allows the possibility to adjust or improve pellet properties with spheronization variables ("flexibility").

Whatever the extrusion system, the industrial scale led globally to a very slightly improved system robustness, and lower flexibility, compared to lab scale.

At lab scale, the results are not statistically all analyzable (notably elongation and usable yield for axial

Table 3. Detailed experimental design analysis by scale and extrusion system. Study of robustness (A and/or C = NS) and flexibility (B = ↗ or ↘).

	Lab scale						Industrial scale					
	Radial			Axial			Radial			Axial		
Responses	**A**	**C**	**B**	**A**	**C**	**B**	**A**	**C**	**B**	**A**	**C**	**B**
Y1	↗	↗	NS	NS	↗	NS	↘	↗	NS	NS	NS	NS
Y2	↗	NS	NS	↗	↗	NS	↘	↗	NS	NS	↗	NS
Y3	↘	↗	↗	↗	↗	↗	↘	↗	NS	↗	NS	NS
Y4	NS	↘	↘	↗	NS	↘	↘	NS	↘	NS	↗	↘
Y5	NS	↘	↘	NS	NS	↘	NS	NS	NS	↗	↗	↘
Y6	↗	↗	↗	NS	NS	NS	↗	↗	NS	↘	NS	NS
Y7	NS	↗	↗	NS	↗	NS	NS	↗	NS	NS	↗	NS
Y8	↘	↘	NS	↘	↘	NS	NS	↘	NS	NS	↘	NS
Y9	NS	↘	NS	NS	NS	NS	↘	↘	NS	NS	NS	NS
Y10	↘	NS	NS	↘	↘	NS	↘	↗	NS	NS	↘	NS

NS = no significant effect of the factor on the response.
↗ = the value of the response significantly increases with the factor (*i.e.* when the factor increases).
↘ = the value of the response significantly decreases with the factor (*i.e.* when the factor decreases).
A = DS concentration, B = Spheronization time, C = DS solubility.
Y values are defined in Figure 1.

system), but a previous study showed that radial system presented the best robustness and flexibility[13]. Conversely, at industrial scale, axial system presented the best robustness (with more particularly an absence of impact of drug solubility on pellet size) and a slightly better flexibility (even if this one is limited at industrial scale).

Conclusion

Compared to lab scale, the conclusions observed at industrial scale are the same in terms of product quality (axial system giving better results), and different in terms of robustness and flexibility (axial system being better at industrial scale, conversely to radial system at lab scale), which confirms the importance to test the two systems at industrial scale before investing in one industrial equipment.

Considering the results, axial system appears as the system giving the best results, and the easiest scaled-up one, without any process or formulation readjustment, by comparison with lab scale. The design of experiments approach thus allowed studying critical parameters and their interactions on the different responses, and identifying the more efficient extrusion system, through different design analyse.

Experimental designs allow building design spaces where selected responses are into specifications whatever the formulation and/or process parameters. It firstly evaluates potential risks in scale-up operation: if the design space is applicable to multiple operational scales, it is described in terms of relevant scale-independent parameters. It also evaluates the ability of the process to tolerate variability of materials and changes in the process and equipment without negative impact on quality. It thus enters in quality risk management, in a quality by design context.

Declaration of interest

The authors report no conflicts of interest.

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