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Surface responses and desirability functions to determine optimal granulation domains

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Abstract

Background: Single pot mixer–granulator–dryer (high-shear granulator with in situ double jacket vacuum drying) and multiphase equipments (high-shear granulator associated with fluid bed dryer) are classically used for wet granulation. At present time, industrial production imperatives may require to switch one formulation from one equipment to another. *Method*: To compare the two processes and to define, for each of them, the optimal formulation domain, experiments were organized according to Doehlert experimental designs. Response surfaces were used to identify the levels of each factor (binder and filler ratios) inducing the more satisfying responses. The contribution of binder and filler ratios to granule properties was highlighted according to the process. Then the desirability function was used to determine and compare the optimal formulation domain for each process. *Results and conclusion*: In the studied formulation domain and for the considered equipments, the transposition from a single pot to a multiphase high-shear granulation process did not seem to raise difficulties; the same formulations were out of specification for both processes and other trials, the technological properties were maintained or improved in the Fielder®/Niro® equipment.

Key words: *Desirability function; Doehlert experimental design; high-shear wet granulation; multiphase process; response surfaces; single pot process*

Introduction

High-shear wet granulation is usually performed in the pharmaceutical industry to improve homogeneity, flow properties, and compressibility of powders. The granule characteristics are controlled by combining formulation and the process parameters. A granulation solution is added to the mechanically agitated powder mix, which results in size enlargement by the formation of liquid bridges between primary particles. The powder mix is agitated by a mixer arm that rotates at high speed in the bowl and a chopper acts as a breakage device. Among high-shear granulation processes, multiphase equipment such as a high-shear granulator associated to a fluid bed dryer remained a very common configuration. However, single pot mixer–granulator–dryers have also been seen as an interesting alternative[1–4].

At this time, because of production equipment renewal or production site transfer, switching from one equipment to another may be necessary. In that case, granule end-use properties have to be kept constant. Many difficulties are likely to arise because of the numerous process (granulation and drying) and formulation parameters that must be taken into account[5].

Previous studies have shown the respective effect of granulation equipment[6,7] and drying process[8,9] on particle and tablet properties, at pilot and industrial scale.

The feasibility of a switch from a single pot to a multiphase process was demonstrated for a model excipient formulation applied to two drug substances (DSs) (differing mainly on their solubility) at two concentrations (1% and 25%) and was confirmed when varying the excipient formulation.

The aim of this study was to highlight the evolution of granule and tablet properties (granule size dispersion,

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porosity, flow rate, Carr index, and characteristic dissolution time) according to the formulation parameters. Response surface method is widely used to determine and compare optimal domains[10–19].

The desirability function approach[20,21] is a complementary method used for the optimization of process involving multiple responses[22–24]. This method consists of transforming each response into a desirability value according to the satisfaction level for the considered response; combining the individual desirabilities in an overall desirability allows the multicriteria optimization.

This strategy was used to compare the variations of granule and tablet properties in case of an equipment switch and to determine the optimal formulation domain for each process. This work was performed within the context of the Q8 ICH note[25] concerning pharmaceutical development.

Materials and methods

Materials

Raw materials

The DS was supplied by Les Laboratoires Servier (Oril, Bolbec, France). Its water solubility was 0.140 g/L, and the median particle diameter was equal to 13 µm with a dispersion of 2.3. As internal phase of the formulation, DS (at a concentration of 25%), lactose monohydrate (Lactose regular®110M HMS, $d_{0.5} = 75.7 \pm 0.8$ µm, $d_g = 2.6$), corn starch Extra Blanc® (Roquette, Frères, Lestrem, France; $d_{0.5} = 13.4 \pm 0.2$ µm, $d_g = 0.9$), and povidone (Kollidon® K30, BASF, Levallois Perret, France; $d_{0.5} = 58.7 \pm 0.6$ µm, $d_g = 2.0$) were used.

Sodium starch glycolate (Primojel®; AVEBE, Evry, France), magnesium stearate (MF3; Quindis, Levallois Perret, France), stearic acid (Stearine TP® micronized; Laserson S.A., Etampes, France), and colloidal anhydrous silica (Aerosil 200®, Laserson SA, Etampes, France) were added to the final granulated blend as the external phase. The different excipient ratios that were tested are detailed in Table 1. The adjustment to 100% was done with the filler.

Table 1. Drug substance and excipient ratios.

	Ratios (%)
DS	25
PVP K30[V]	2–6–10
Corn starch	*
Lactose/mannitol (100/0; 75/25; 50/50; 25/75; 0/100)	Up to 100
Sodium starch glycolate	*
Colloidal anhydrous silica	*
Magnesium stearate	*
Stearic acid	1.1–1.75–2.4

*These excipients were employed in fixed ratios corresponding to their common pharmaceutical use as binder, disintegrant, and lubricant[26].

Equipment

Single pot mixer–granulator–dryer: Moritz® Turbosphere TS50. The Moritz® (Bio-inox, Orléans, France) Turbosphere TS50 is a single pot system, that is, mixing, granulation, and drying are performed in the same apparatus. It is a pilot scale equipment with a 50 L spherical bowl for a nominal capacity of approximately 20 kg granule batches. It is equipped with a three-blade impeller and a twin-shell chopper. The impeller design is adapted to the spherical shape of the bowl to improve the volume of powder swept by the mixing tool and to decrease wall adhesion and dead zones. Conduction drying occurs in situ using the heated double jacket and the vacuum system.

Multiphase equipment: Fielder® PMA 65/Niro®. The Fielder® PMA65 is a vertical shaft high-shear mixer granulator equipped with a vertical three-blade impeller and an horizontal U-shaped chopper. It is a pilot scale equipment with a 65 L conical bowl for a nominal capacity of approximately 20 kg granule batches.

The fluid bed dryer used was an Niro MP2®. Product, inlet air, and outlet air temperatures were measured using temperature probes. Inlet air velocity was also controlled.

Methods

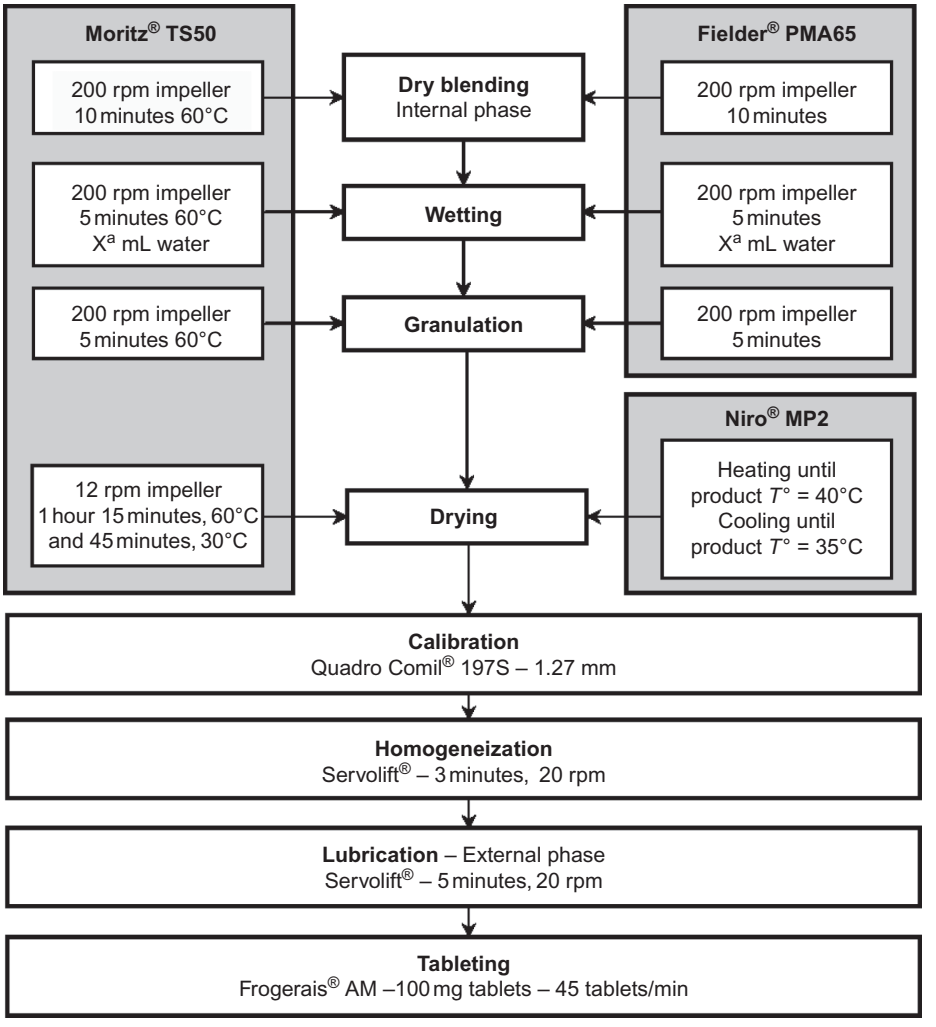
Granule and tablet preparation

Process conditions were fixed according to the flow chart presented in Figure 1. Twenty kilograms of the internal phase was dry mixed, either in the Moritz® Turbosphere TS50 or in the Fielder® PMA65 granulator.

Distillated water was added as granulation liquid. The volume of granulation liquid was adjusted for each formulation and for each granulation equipment to obtain a granule median diameter of about 150 µm (between 130 and 180 µm) to be close to industrial conditions required for further tableting. Nevertheless, this diameter could not be obtained for each trial, depending on the formulation.

Based on the granulation equipment, granules were dried in situ by double jacket vacuum drying or in a fluid bed dryer (Niro® MP2) until a final moisture content between 2% and 3% was reached. Loss on drying was measured on 5-g samples heated at 105°C for 10 minutes using a Mettler LP16 infrared desiccator (Mettler Instrument®, Viroflay, France).

After lubrication, tableting was performed on an alternative tableting machine (Frogerais® AM) equipped with 6 mm diameter punches with a radius of curvature of 6, at a compression speed of 45 tablets per minute. The unitary mass of the tablets was fixed at 100 mg. Compression force was adjusted to obtain tablets with a maximum breaking force of 35 N.



[a]Granulation liquid was always added in 5 minutes in all experiments by varying the liquid addition rate.
[b]Product *T*°: product temperature measured using a temperature probe.

Figure 1. Granulation, drying, and tableting flow chart.

Granule and tablet characterizations

Granule size distribution. Granule size distribution was determined by laser diffraction (Mastersizer 2000; Malvern Instruments, Worcestershire) equipped with a dry-powder dispersing system (Scirocco 2000). Analyses were performed in triplicate at a dispersion pressure of 1 bar. Particle size distributions were characterized by their volume median diameter ($d_{0.5}$) and dispersion (d_g).

The dispersion of the distribution (d_g) was calculated from $d_{0.5}$, $d_{0.1}$, and $d_{0.9}$ according to the following equation:

$$d_g = \frac{d_{0.9} - d_{0.1}}{d_{0.5}}, \quad (1)$$

where $d_{0.1}$ and $d_{0.9}$ values are the particle diameters corresponding to 10% and 90%, respectively, of the cumulative distribution. Granule size dispersion was required to be as narrow as possible, which is expressed by a low d_g value (<3).

Bulk and tapped densities. Bulk (D_{bulk}, g/cm^3) and tapped (D_{tapped}, g/cm^3) densities were determined using a 250 mL graduated cylinder (Erweka Model SVM2; Erweka GmbH, Heusenstamm, Germany) according to the European Pharmacopeia (Ph. Eur. 2.9.15) on 100 g of powder. The expressed results corresponded to the average of three measurements.

Porosity. The porosity of granules was calculated from their pycnometric (D_{pycno}) and tapped (D_{tapped}) densities[7,27] according to the following equation:

$$e = \left(\frac{1 - D_{\text{tapped}}}{D_{\text{pycno}}} \right) \times 100 \quad (2)$$

Flowability. Flow rate was measured in accordance with the European Pharmacopeia (Ph. Eur. 2.9.16) on 100 g of powder. The expressed results corresponded to the average of three measurements. A flow rate higher than 10 g/s corresponded to good flow properties.

Carr index. The Carr index was used to express granule packing ability. It was determined according to the European Pharmacopeia (Ph. Eur. 2.9.36)[28]; a Carr index lower than 20% corresponded to good packing properties.

Mechanical properties. The behavior under pressure of lubricated granules was studied using an instrumented alternative tableting machine (Korsch EK0, Korsch Maschinenfabrik, Germany) equipped with 1 cm^2 punches. The volume of the compression chamber was fixed at 1 cm^3.

Tensile strength. Tensile strength (Rd, MPa) was calculated for the tablets manufactured at 150 MPa[29,30] according to the following equation:

$$\text{Rd} = \frac{2F}{\pi dh}, \quad (3)$$

where $F(N)$ is the maximal diametral breaking force, d (mm) the diameter, and h (mm) the height of the tablet.

Residual lower punch pressure. The residual lower punch pressure (P_{R150}, MPa), that is, the pressure remaining on the lower punch when the upper punch is no longer in contact with the compacted powder, was determined, to quantify tablet sticking. The measurement was performed on tablets manufactured at 150 MPa. A P_{R150} lower than 10 MPa indicated a suitable lubrication and was especially efficient when P_{R150} was lower than 5 MPa. On the contrary, a P_{R150} value greater than 10 MPa revealed a poor lubrication efficiency with a sticking phenomenon during compression[31].

Dissolution kinetics. Dissolution kinetics was determined on 6 mm diameter tablets ($n = 6$) with a radius of curvature of 6 and a mean maximum breaking force around 35 N. Studies were performed in 500 ± 5 mL of a 0.01 N HCl solution as recommended for immediate release dosage forms (Ph. Eur. 2.9.3) using the automatic paddle apparatus Sotax AT70 Smart with in-line UV detection (Sotax®, Saint-Louis, France) (Ph. Eur. 2.9.3). Stirring speed was fixed at 100 rpm. Samples were taken after 5, 10, 15, 30, 45, and 60 minutes. The concentration of DS was measured by UV detection at a wavelength of 230 nm.

Dissolution kinetics was fitted with the Weibull model[32,33]. TW80 represented the time required to dissolve 80% of the DS. As this study concerned immediate release tablets, the specification retained was TW80 lower than 30 minutes.

Table 2. Studied parameters and specifications.

	Studied parameters	Specifications (when relevant)
Granule size distribution	Size dispersion: d_g	<3
Porosity	Calculated porosity: e (%)	
Packing ability	Carr index: I_{Carr} (%)	<25%
Flow ability	Flow rate (g/s)	>10 g/s
Mechanical properties	Tensile strength: R_{d150} (MPa)	>0.30 MPa
	Residual lower punch pressure: PR_{150} (MPa)	<16 MPa
Dissolution kinetics	Time required to dissolve 80% of the drug substance: TW80 (min)	<30 minutes

Table 2 summarizes granule and tablet characterization methods and the corresponding studied parameters. Specifications are indicated, when relevant.

Description of the Doehlert experimental design

Our aim was to compare the two processes (single pot versus multiphase) on granule and tablet properties, according to formulation parameters, filler (lactose/mannitol), binder (PVP), and lubricant (stearic acid) ratios.

Experiments were planned according to three Doehlert experimental designs[34] (presented in Figure 2) with two factors at three levels and one factor at five levels as listed in Table 1. The design was composed of 21 points uniformly distributed in each layer. The same experimental design was repeated for each process (single pot and multiphase). Such design allows the elaboration of a second-order polynomial equation, the construction of response surfaces, and the determination of the optimal formulation domain.

The desirability function

The desirability value is a satisfaction index ranging between 0 and 1, characterizing the level of a response considering a particular objective[35]. For the optimization of a process involving multiple responses, the individual responses have to be combined to define a product with the desired characteristics. The desirability value[20,21] is used to classify experiments according to the degree of satisfaction. In this study, a linear desirability function $\mathcal{D}_{Y_i} = f(Y_i)$ between a limit and a target value was used for all the responses (Figure 3).

For each response (Y_i), the desirability function $\mathcal{D}(Y_i)$ assigns values from 0 and 1 to the possible values of Y_i; $\mathcal{D}(Y_i) = 0$ corresponding to a completely undesirable value of Y_i and $\mathcal{D}(Y_i) = 1$ corresponding to

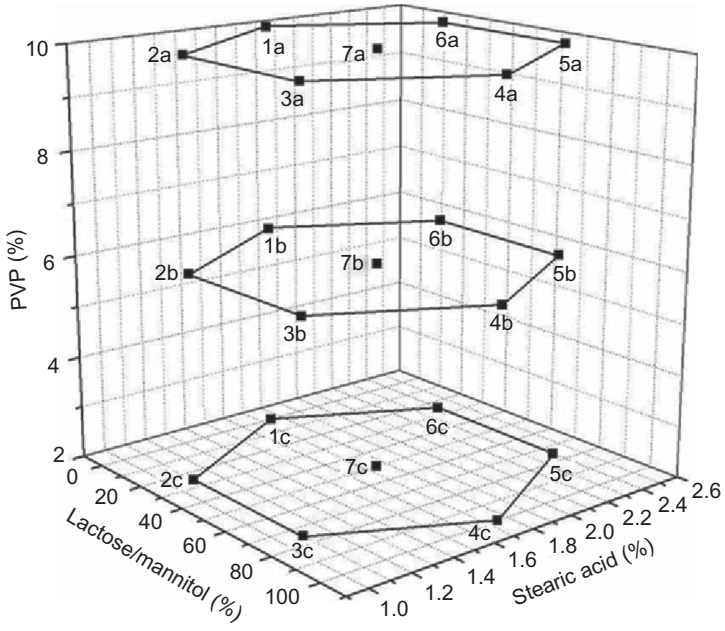


Figure 2. Doehlert uniform shell design.

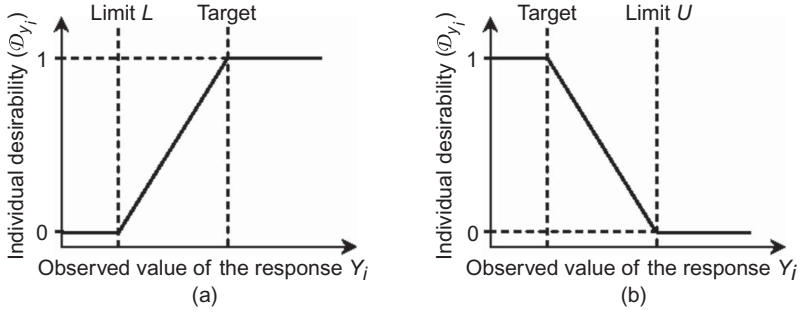


Figure 3. Schematic representations of the individual desirability function ($\mathcal{D}_{Y_i}$).

a completely desirable or ideal response value. Two desirability functions $\mathcal{D}(Y_i)$ were used depending on whether the response Y_i had to be maximized (Figure 3, case a) or minimized (Figure 3, case b) up to a target value (T)[21].

The limit (L) is the Y_i value under which the desirability is equal to 0 and the target (T) is the Y_i value for which the maximum desirability is reached. These limit and target values, used for the calculation of the individual desirability ($\mathcal{D}_{Y_i}$), are listed in Table 3. The responses were selected for this part of the analysis to propose an overall desirability value (geometric mean of the individual desirabilities), which considers together the main characteristics of granules (size distribution, flow, and packing ability) and tablets (sticking during compression, tensile strength, and dissolution kinetics) necessary to be taken into account to define the global quality of the production.

Table 3. Target (T) and limit (upper U or lower L) values of the parameters used for the calculation of the desirability function.

	Y_i	Upper (U) or lower (L) limit	Target value (T)
Responses to be maximized	Flow rate (g/s)	$L = 10$	20
	Tensile strength (MPa)	$L = 0.3$	1
Responses to be minimized	Dispersion	$U = 3$	1.5
	Carr index (%)	$U = 25$	15
	Residual lower punch pressure (MPa)	$U = 15$	10
	Dissolution time, TW80 (min)	$U = 30$	15

The choice was dependent on both regulatory and internal industrial specifications.

Flow rate and tensile strength desirability values were calculated using the function a of Figure 3 as a high flow rate value corresponded to good flow properties and the tensile strength of the granules needed to be high enough for tablet handling. The desirability function of these parameters was calculated using Equation (4):

$$\mathcal{D}_{\text{Flow rate,}}\,\mathcal{D}_{\text{Rd150}} = \frac{Y_i - L}{T - L}, \tag{4}$$

where $D_{\text{Flow rate}}$ is the individual desirability of granule flow rate and D_{Rd150} is the individual desirability of tablet tensile strength. L is the lower limit value below which the desirability is equal to 0 and T is the target value from which the desirability is 1.

The individual desirability of granule size dispersion (d_g), Carr index (I_{Carr}), residual lower punch pressure (PR_{150}), and characteristic dissolution time (TW80) values were calculated using the function b of Figure 3, as granule size dispersion needs to be as narrow as possible, a low Carr index expresses good packing ability, sticking in the die during compression has to be minimized, and dissolution time of immediate release tablets must be as fast as possible. The calculation of the desirability function was carried out using Equation (5):

$$\mathcal{D}_{\text{dg}}, \mathcal{D}_{\text{ICarr}}, \mathcal{D}_{\text{PRI50}}, \mathcal{D}_{\text{TW80}} = \frac{U - Y_i}{U - T}, \tag{5}$$

where $\mathcal{D}_{\text{dg}}$, $\mathcal{D}_{\text{ICarr}}$, $\mathcal{D}_{\text{PR150}}$, and $\mathcal{D}_{\text{TW80}}$ are, respectively, the individual desirabilities of granule size distribution, Carr index, residual lower punch pressure, and characteristic dissolution time. U is the upper limit value from which the desirability is null and T is the target value below which the desirability is 1.

The overall desirability ($\mathcal{D}$) is calculated using Equation 6:

$$\mathcal{D} = (\mathcal{D}_{\text{dg}} \times \mathcal{D}_{\text{Flow rate}} \times \mathcal{D}_{\text{ICarr}} \times \mathcal{D}_{\text{Rd150}} \times \mathcal{D}_{\text{PR150}} \times \mathcal{D}_{\text{TW80}})^{1/6}. \tag{6}$$

The different experiments will be classified according to this value.

Results and discussion

Raw data concerning granule and tablet properties are presented in Tables 4 and 5, respectively, for TS50® and Fielder®/Niro® granules.

Study of the influence of excipient ratios on granule properties

The variation of the responses as a function of the studied filler, binder, and lubricant ratios was displayed using response surfaces, which were built using a second-order polynomial model. Coefficients of determination (r^2) ranging from 0.31 to 0.95 were obtained, indicating that only a part of the variation in the data could be explained by the chosen parameters. The best overall model fits were observed for granule size distribution: d_g ($r^2_{\text{TS50}®} = 0.81$; $r^2_{\text{Fielder}®/\text{Niro}®} = 0.72$); porosity: e ($r^2_{\text{TS50}®} = 0.95$; $r^2_{\text{Fielder}®/\text{Niro}®} = 0.56$); and Carr index: I_{Carr} ($r^2_{\text{TS50}®} = 0.56$; $r^2_{\text{Fielder}®/\text{Niro}®} = 0.83$).

As granule characteristics were determined on nonlubricated granules, they were not linked to the stearic acid ratio that was added in the external phase. Each studied response was presented according to lactose/mannitol (filler) and PVP (binder) ratios only.

As shown by the response surface (Figure 4), the evolution of the granule size dispersion was similar whatever the granulation process was. A quite higher granule size dispersion (expressed by a higher value of dg) was observed for TS50® granules probably in relation with the attrition phenomenon occurring during the rather long drying time under kneading[36,37]. Whatever the process, the weaker granule size dispersion was obtained for granules formulated with 6% of binder. Granule size dispersion increased when the lowest amount of PVP was used, corresponding to inefficient granulation which also led to a median diameter lower than 130 μm (Tables 4 and 5). The median diameter was higher for granules formulated with 10% of PVP but the wide size distribution may suggest higher granule friability. Granule size dispersion was not dependent on the lactose/mannitol ratio.

Granule porosity data ranged from 44% to 52% for both processes (Tables 4 and 5); nevertheless, their evolution according to the excipient ratios was highly dependent on the process. The analysis of surface responses (Figure 5) showed that the porosity of TS50® granules increased quite linearly ($r^2 = 0.94$) with the PVP ratio, but no influence of the lactose/mannitol ratio was observed. On the contrary, the porosity of Fielder®/Niro® granules was dependent on both lactose/mannitol and PVP ratios. The granule bed porosity was the smallest for 6% PVP and for high ratios of lactose. These observations were probably in relation with granule shape and texture that may differ from one granulation equipmenz to another as shown by Hegedűs and Pintye-Hódi[9] when comparing Collette ultima 600 and Diosna P400 high-shear granulator.

Carr indexes of single pot granules were higher than multiphase ones and they were independent of lactose/mannitol and PVP ratios. In the case of Fielder®/Niro®

Table 4. Characteristics of granules manufactured in TS50® and corresponding tablets.

Factors/ levels					Responses						
					Unlubricated granules				Tablets		
Exp. no.	PVP	Lactose/ mannitol	Stearic acid	$d_{0.5}$ (µm)	d_g	e (%)	Flow rate (g/s)	I_{Carr} (%)	Rd_{150} (MPa)	P_{R150} (MPa)	TW80 (min)
1a	10	0/100	100	152 ± 1	2.3 ± 0.1	50	19 ± 0	21 ± 1	1.04 ± 0.03	13.4	20.1
1b	6	0/100	100	145 ± 3	2.5 ± 0.1	48	19 ± 0	20 ± 1	0.91 ± 0.04	18.3	15.6
1c	2	0 /100	100	75 ± 1	3.2 ± 0.0	45	0 ± 0	22 ± 0	0.60 ± 0.02	21.3	25.9
2a	10	25/75	75	149 ± 0	2.9 ± 0.0	49	19 ± 1	21 ± 1	0.53 ± 0.01	18.8	19.6
2b	6	25/75	75	147 ± 2	2.2 ± 0.0	47	20 ± 0	22 ± 0	0.81 ± 0.04	20.1	25.5
2c	2	25/75	75	80 ± 1	3.0 ± 0.1	44	0 ± 0	22 ± 0	0.55 ± 0.05	21.3	24.9
3a	10	75/25	25	164 ± 2	2.1 ± 0.1	50	20 ± 0	20 ± 1	0.71 ± 0.04	10.9	29.3
3b	6	75/25	25	154 ± 2	2.1 ± 0.1	46	21 ± 0	22 ± 0	0.81 ± 0.03	20.1	29.9
3c	2	75/25	25	85 ± 1	2.8 ± 0.0	45	0 ± 0	22 ± 1	0.65 ± 0.03	19.8	22.8
4a	10	100/0	0	165 ± 1	1.9 ± 0.0	49	21 ± 0	20 ± 1	0.85 ± 0.03	11.4	29.9
4b	6	100/0	0	138 ± 0	2.0 ± 0.0	46	20 ± 1	21 ± 0	0.75 ± 0.02	14.6	29.3
4c	2	100/0	0	90 ± 4	3.0 ± 0.1	45	0 ± 0	21 ± 0	0.70 ± 0.00	17.6	24.7
5a	10	75/25	25	164 ± 5	2.1 ± 0.3	50	20 ± 0	20 ± 1	0.91 ± 0.07	12.6	28.3
5b	6	75/25	25	154 ± 1	2.1 ± 0.2	46	21 ± 0	22 ± 0	0.81 ± 0.00	14.1	30.0
5c	2	75/25	25	85 ± 3	2.8 ± 0.3	45	0 ± 0	22 ± 0	1.01 ± 0.03	12.9	28.0
6a	10	25/75	75	149 ± 2	2.9 ± 0.1	49	19 ± 0	21 ± 1	0.73 ± 0.04	8.7	23.9
6b	6	25/75	75	147 ± 2	2.2 ± 0.1	47	20 ± 0	22 ± 0	0.81 ± 0.03	15.0	28.8
6c	2	25/75	75	80 ± 1	3.0 ± 0.0	44	0 ± 0	22 ± 1	0.68 ± 0.03	17.6	29.6
7a	10	50 /50	50	156 ± 0	2.4 ± 0.0	49	21 ± 1	19 ± 1	0.89 ± 0.03	13.6	29.4
7b	6	50/50	50	150 ± 2	2.4 ± 0.0	47	20 ± 0	20 ± 0	0.82 ± 0.05	14.9	29.9
7c	2	50/50	50	90 ± 1	3.4 ± 0.1	44	0 ± 0	23 ± 0	0.65 ± 0.07	21.3	23.9

Table 5. Characteristics of granules manufactured in Fielder® PMA 65 and dried in Niro® fluid bed dryer and corresponding tablets.

Factors/ levels					Responses						
					Unlubricated granules				Tablets		
Exp. no.	PVP	Lactose/ mannitol	Stearic acid	$d_{0.5}$ (µm)	d_g	e (%)	Flow rate (g/s)	I_{Carr} (%)	Rd_{150} (MPa)	P_{R150} (MPa)	TW80 (min)
1a	10	0/100	1.75	180 ± 8	1.7 ± 0.2	48	17 ± 1	16 ± 1	1.01 ± 0.02	11.5	29.7
1b	6	0/100	1.75	128 ± 5	1.9 ± 0.0	47	19 ± 1	20 ± 0	0.72 ± 0.06	15.1	22.4
1c	2	0 /100	1.75	72 ± 1	3.0 ± 0.1	52	0 ± 1	20 ± 1	0.85 ± 0.02	17.9	32.0
2a	10	25/75	1.1	169 ± 9	2.2 ± 0.3	49	20 ± 1	16 ± 1	0.79 ± 0.18	14.8	23.6
2b	6	25/75	1.1	143 ± 5	1.6 ± 0.0	47	18 ± 2	18 ± 0	0.71 ± 0.01	9.5	26.3
2c	2	25/75	1.1	89 ± 2	2.6 ± 0.1	50	0 ± 0	20 ± 1	0.81 ± 0.08	15.3	16.7
3a	10	75/25	1.1	180 ± 3	1.8 ± 0.0	45	16 ± 2	14 ± 1	0.68 ± 0.01	15.6	29.5
3b	6	75/25	1.1	154 ± 4	1.6 ± 0.0	45	22 ± 0	18 ± 0	0.58 ± 0.02	15.9	29.3
3c	2	75/25	1.1	92 ± 1	2.7 ± 0.0	47	0 ± 0	21 ± 0	0.49 ± 0.02	19.8	15.1
4a	10	100/0	1.75	175 ± 11	1.6 ± 0.1	47	21 ± 1	16 ± 1	0.65 ± 0.01	11.6	22.5
4b	6	100/0	1.75	150 ± 3	1.7 ± 0.0	46	22 ± 1	19 ± 0	0.53 ± 0.00	13.1	16.6
4c	2	100/0	1.75	107 ± 2	2.6 ± 0.1	48	0 ± 0	20 ± 0	0.52 ± 0.03	15.1	20.3
5a	10	75/25	2.4	180 ± 3	1.8 ± 0.1	45	16 ± 0	14 ± 1	0.94 ± 0.03	9.7	26.6
5b	6	75/25	2.4	154 ± 3	1.6 ± 0.0	45	22 ± 0	18 ± 0	0.74 ± 0.04	15.9	29.9
5c	2	75/25	2.4	92 ± 1	2.7 ± 0.0	47	0 ± 0	21 ± 1	0.71 ± 0.04	9.9	24.4
6a	10	25/75	2.4	169 ± 3	2.2 ± 0.0	49	20 ± 1	16 ± 1	0.84 ± 0.12	11.5	39.1
6b	6	25/75	2.4	143 ± 4	1.6 ± 0.0	47	18 ± 0	18 ± 0	0.80 ± 0.03	13.8	29.5
6c	2	25/75	2.4	89 ± 1	2.6 ± 0.0	50	0 ± 0	20 ± 0	0.96 ± 0.07	14.8	24.4
7a	10	50 /50	1.75	173 ± 9	3.1 ± 0.3	47	22 ± 1	18 ± 1	0.84 ± 0.04	14.4	39.4
7b	6	50/50	1.75	147 ± 5	1.9 ± 0.0	47	21 ± 2	19 ± 0	0.67 ± 0.03	14.1	25.1
7c	2	50/50	1.75	83 ± 2	2.9 ± 0.1	47	0 ± 0	21 ± 1	0.64 ± 0.18	13.4	17.7

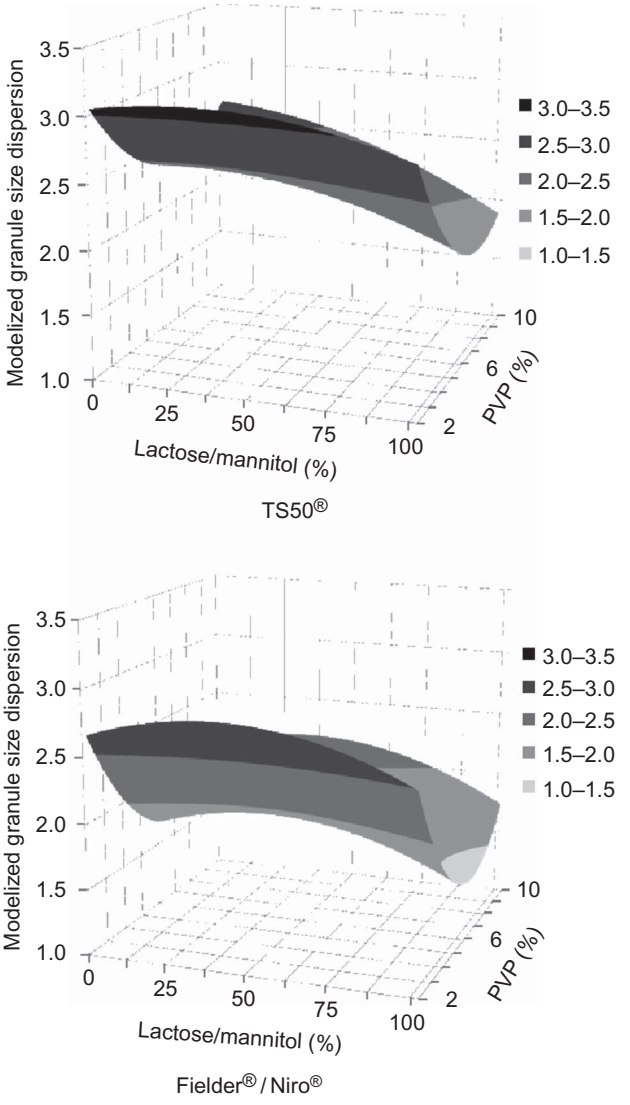


Figure 4. Evolution of size dispersion according to the ratios of lactose/mannitol and PVP.

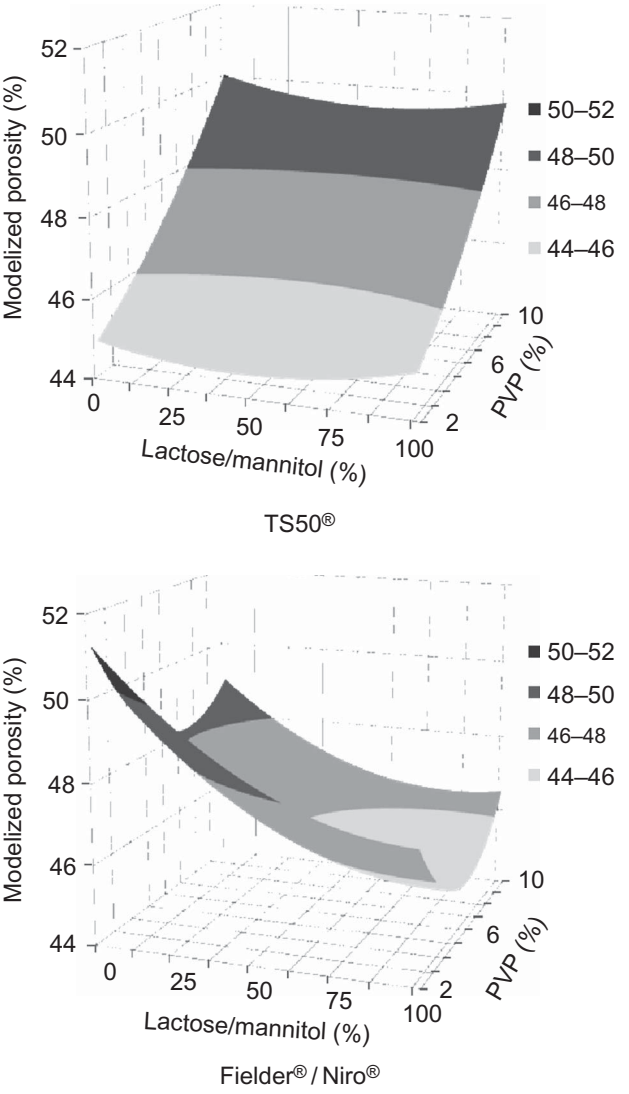


Figure 5. Evolution of porosity according to the ratios of lactose/mannitol and PVP for granules manufactured in TS50® (r^2 = 0.95) and Fielder®/Niro® (r^2 = 0.80).

granules, Carr indexes were influenced by the PVP ratio (Figure 6). They decreased, corresponding to a better compressibility, as the binder ratio increased. The ratio of binder (PVP), responsible for the size distribution of the granules, had also an influence on their rheological properties.

Evaluation of the optimal formulation domains

The domain corresponding to an optimal formulation was determined for each process using the desirability function as the overall desirability ($\mathcal{D}$) combined with the six individual desirability values ($\mathcal{D}_{Y_i}$) in one measurement allowing an easy comparison of the formula. Tables 6 and 7 present the individual and overall desirabilities, respectively, for TS50® and Fielder®/Niro® trials. The repartition of the overall desirability in the experimental domain is shown in Figure 7.

The first observation concerned experiments formulated with 2% of PVP. The overall desirability of all these experiments was null because of a flow rate value equal to 0. These bad flow properties were related to their low median diameter and were relevant whatever the granulation process was (from 75 to 90 µm in TS50® and from 72 to 102 µm in Fielder®/Niro®; Tables 4 and 5). So in the following discussion, only 6% and 10% PVP experiments will be considered.

Concerning TS50® granulations, 10 experiments had a positive desirability. Four of them were formulated with 6% of PVP and the six others with 10% of PVP. The desirability was globally better for 10% PVP experiments.

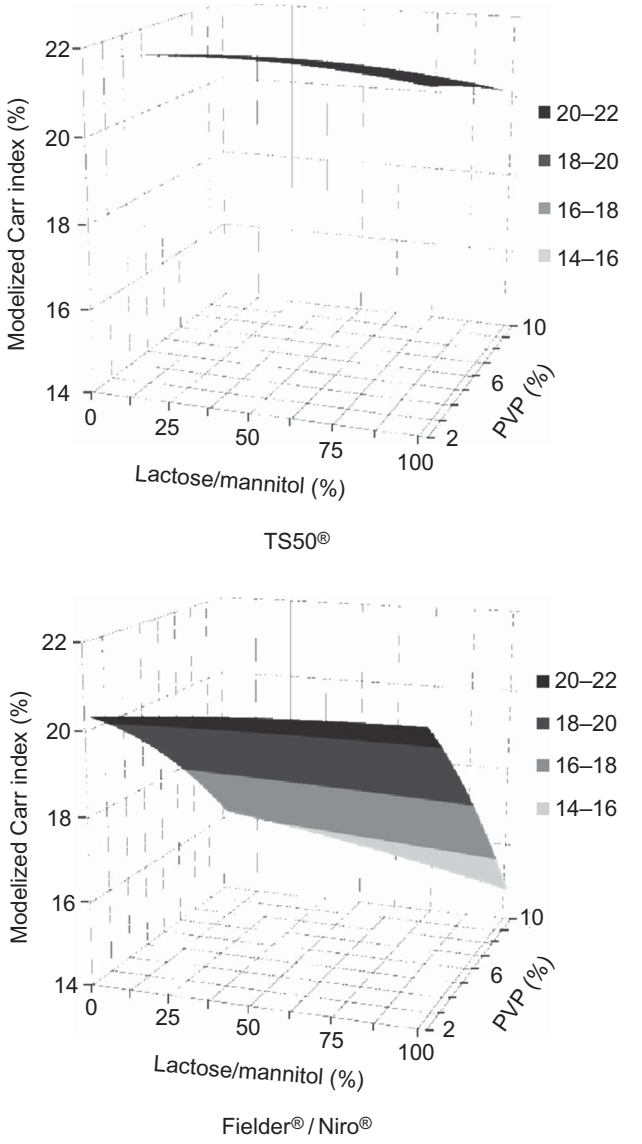


Figure 6. Evolution of the Carr index according to the ratios of lactose/mannitol and PVP for granules manufactured in TS50® (r^2 = 0.56) and Fielder®/Niro® (r^2 = 0.83).

Trials formulated with 6% of PVP presented a TW80 close to the specification limit (30 minutes), expressed by a low value of $\mathcal{D}_{TW80}$, and responsible for an overall desirability decrease. Moreover, the same experiments had also a high value of PR_{150}, because of sticking phenomenon during compression. Globally, for TS50® experiments, the overall desirability increased with PVP ratio.

Concerning Fielder®/Niro® experiments, the desirability was positive for 12 experiments. Seven of them were formulated with 6% of PVP and the five others with 10% of PVP. The experiments with the best overall desirability were evenly distributed between 6% and 10% PVP Doehlert designs suggesting that the optimal PVP ratio could be between these two values. As observed for TS50® trials, the overall desirability was decreased essentially because of the low value of sticking and

Table 6. Individual and overall desirabilities for TS50® experiments.

Exp. no.	Individual desirability values						Overall desirability
	$\mathcal{D}_{dg}$	$\mathcal{D}_{Flow\ rate}$	$\mathcal{D}_{ICarr}$	$\mathcal{D}_{Rd150}$	$\mathcal{D}_{PR150}$	$\mathcal{D}_{TW80}$	$\mathcal{D}$
1a	0.50	0.86	0.41	1.00	0.44	0.66	0.61
5a	0.62	0.97	0.45	0.86	0.56	0.11	0.50
3a	0.62	0.97	0.45	0.59	0.85	0.04	0.43
6a	0.04	0.93	0.39	0.61	1.00	0.40	0.40
7a	0.41	1.00	0.58	0.85	0.40	0.04	0.39
6b	0.55	0.99	0.34	0.73	0.17	0.08	0.35
4a	0.76	1.00	0.50	0.79	0.77	0.01	0.35
4b	0.65	1.00	0.36	0.65	0.23	0.05	0.34
7b	0.41	1.00	0.45	0.74	0.18	0.01	0.24
5b	0.59	1.00	0.34	0.72	0.31	0.01	0.19
1b	0.32	0.85	0.47	0.87	0.00	0.96	0.00
2a	0.04	0.93	0.39	0.33	0.00	0.69	0.00
2b	0.55	0.99	0.34	0.72	0.00	0.30	0.00
3b	0.59	1.00	0.34	0.74	0.00	0.01	0.00
1c	0.00	0.00	0.28	0.43	0.00	0.28	0.00
2c	0.00	0.00	0.32	0.36	0.00	0.34	0.00
3c	0.12	0.00	0.31	0.50	0.00	0.48	0.00
4c	0.01	0.00	0.40	0.57	0.00	0.35	0.00
5c	0.12	0.00	0.31	1.00	0.52	0.13	0.00
6c	0.00	0.00	0.32	0.55	0.00	0.03	0.00
7c	0.00	0.00	0.24	0.50	0.00	0.40	0.00

Table 7. Individual and overall desirabilities for Fielder®/Niro® experiments.

Exp. no.	Individual desirability values						Overall desirability
	$\mathcal{D}_{dg}$	$\mathcal{D}_{Flow\ rate}$	$\mathcal{D}_{ICarr}$	$\mathcal{D}_{Rd150}$	$\mathcal{D}_{PR150}$	$\mathcal{D}_{TW80}$	$\mathcal{D}$
4a	0.71	1.00	0.89	0.42	0.73	0.50	0.68
5a	0.60	0.63	1.00	0.90	1.00	0.22	0.65
2b	0.68	0.76	0.70	0.52	1.00	0.25	0.60
4b	0.67	1.00	0.64	0.22	0.48	0.89	0.58
2a	0.41	0.99	0.91	0.65	0.20	0.42	0.52
7b	0.53	1.00	0.61	0.44	0.31	0.32	0.49
1b	0.53	0.86	0.53	0.53	0.15	0.51	0.46
1a	0.64	0.67	0.94	1.00	0.75	0.02	0.42
6b	0.68	0.76	0.70	0.66	0.37	0.03	0.37
3a	0.60	0.63	1.00	0.46	0.07	0.03	0.27
5b	0.71	1.00	0.72	0.57	0.02	0.05	0.25
3b	0.71	1.00	0.72	0.30	0.02	0.01	0.18
6a	0.41	0.99	0.91	0.74	0.75	0.00	0.00
7a	0.00	1.00	0.68	0.73	0.27	0.00	0.00
1c	0.01	0.00	0.51	0.74	0.00	0.00	0.00
2c	0.19	0.00	0.46	0.68	0.11	0.88	0.00
3c	0.16	0.00	0.39	0.16	0.00	0.99	0.00
4c	0.20	0.00	0.50	0.19	0.15	0.64	0.00
5c	0.16	0.00	0.39	0.52	1.00	0.38	0.00
6c	0.19	0.00	0.46	0.94	0.20	0.37	0.00
7c	0.03	0.00	0.39	0.40	0.44	0.82	0.00

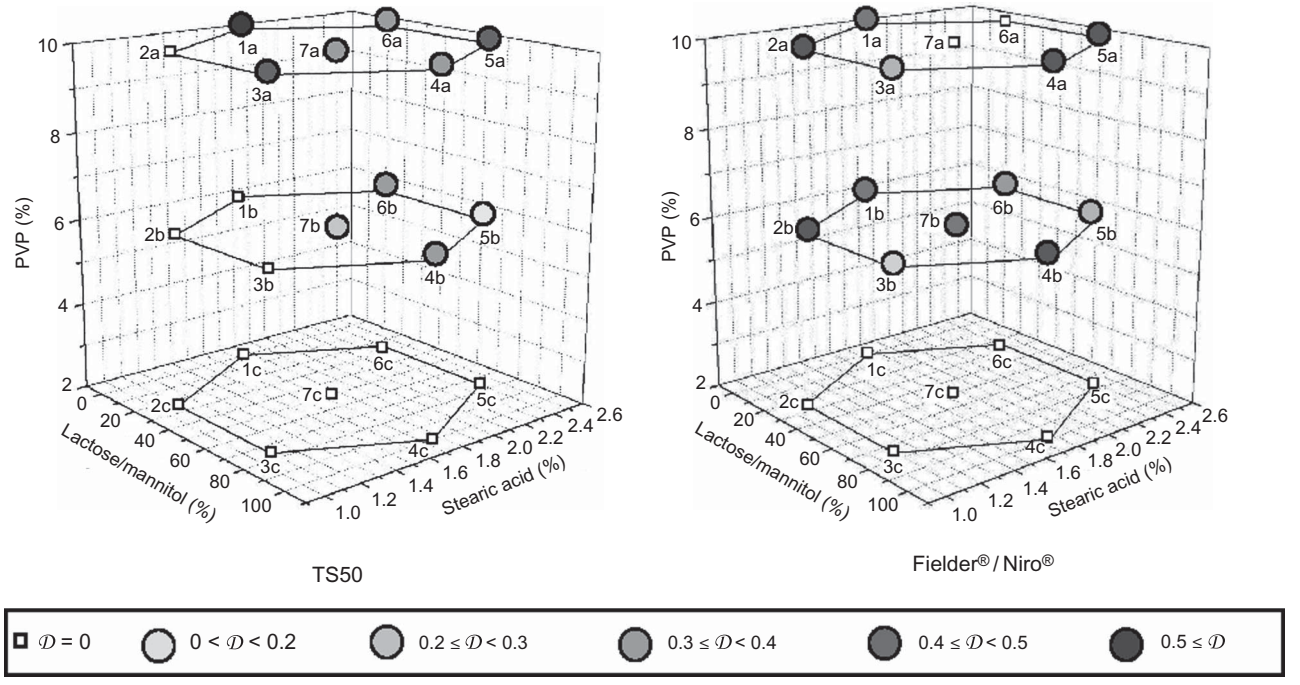


Figure 7. Visualization of overall desirabilities at each point of the experimental domain.

dissolution desirabilities. Nevertheless, as opposed to TS50® trials, this observation was independent of the binder ratio. Moreover, the results seemed to be globally improved when one of the two fillers was in a major proportion in the formula.

The optimal formulation domains included the highest binder concentrations for both processes, but the overall desirabilities were found to be improved for Fielder®/Niro® trials compared to TS50® ones: five Fielder®/Niro® formulations presented an overall desirability higher than 0.5 whereas only one TS50® overall desirability reached this value. Let us remind that the compressibility evaluation was based on laboratory compression test, carried out on an alternative tableting machine. It might be careful to confirm these conclusions by testing the granule behavior on a rotative tableting machine to take into account compression rate effect and sticking phenomenon that may occur in industrial conditions.

Conclusion

Response surfaces were used to identify the levels of each factor (binder and filler ratios) inducing the more satisfying responses. The desirability function completed the observations by pointing out the optimal formulation area of each process.

The evolution of the granule size dispersion was found to be independent of the process but dependent on the binder ratio with narrower dispersion for 6% PVP formulations. On the contrary, the evolution of granule porosity and Carr index with the formulation was shown to differ from one process to the other.

The desirability function allowed a classification of the experiments according to key characteristics (granule size dispersion, flow rate, Carr index, tablet sticking during compression, tensile strength, and characteristic dissolution time, i.e., TW80) chosen for their relevance in describing granule and tablet quality, in reference to regulatory and internal specifications. The optimal formulation domain of each process was found to be strongly linked to the binder ratio (particularly for TS50® experiments) and to a smaller extent to the lactose/mannitol ratio. The ratio of lubricant was not found to be an influent factor in the studied domain. Nevertheless, the sensitivity to formulation change was quite different for the two processes; in particular higher binder content was required for TS50® trials compared to Fielder®/Niro® ones.

In the studied formulation domain and for the considered equipments, the switch from the single pot to the multiphase high-shear granulation process did not seem to raise difficulties, as the multiphase process was shown to lead to the same out of specification formulations and was likely to improve the acceptable ones.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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