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Research paper

Construction of a quality index for granules produced by fluidized bed technology and application of the correspondence analysis as a discriminant procedure

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ABSTRACT

The production of granules by wet granulation in a fluidized bed was assessed after the construction of a quality index based on a file of attributes (relevant factors). These attributes are combined by a methodology relying on Correspondence Analysis, as a discriminant procedure, using two extreme simulated active vectors representing, respectively, the best and the worst cases for the granules quality output ("bad" and "good" pole). From those, a single continuous synthetic variable – the quality index – can be produced referring to a more significant set of samples. As an application of the methodology, the work compares the quality of granules produced at a laboratory scale and a pilot scale. The factors contribution to the bad or good pole allowed the identification of the most relevant factors that affect the quality of the granules. The factors studied, according to a center of gravity design, included formulation (solubility of a drug, different grades of polyvinylpyrrolidone, the polarity of the granulation solution) and processing factors (the rate of administration of the granulation solution, the atomizing air pressure and the fluidizing air rate). Granules were evaluated for production yield, drug content, size, densities (true, bulk and tapped), friability, flowability and compressibility. The study has emphasized the differences between the laboratory and pilot scales and the relative importance of each factor for the quality of the granules produced.

1. Introduction

The production of granules by wet granulation is an important operation in the pharmaceutical industry to minimize several physical and technological related limitations of many drugs. Granulation of powders improves their compressibility and compactibility, promotes a better handling as a consequence of a higher control over the product's bulk density (even for high drug contents), narrows the size distribution of the particles produced and provides a better control of the drug's content uniformity at low drug concentrations [1]. It must be pointed out that on top of the mechanical properties mentioned, granules should present other properties with clinical impact (e.g. strength, activity and controlled drug dissolution rate) within tight specifications that can be difficult to achieve. Although continuous efforts have been made to produce tablets by direct compression, wet granulation to produce granules for compression has not been replaced partly because of development cost considerations and tradition and partly because it remains in some cases an attractive technique, as mentioned by Faure et al. [2]. These authors have considered both formulation and processing conditions and techniques and evaluated their effect on the properties of the granules produced. Litster et al. [3] claimed that the fluid bed granulation is an intrinsically robust process with a limited variation in product quality due to the settling of coarse granules, which never resurface to reach the binder sprayed in an upper position, thus stopping their growth. The complexity of the process of granulation has been recognized by a few authors. Schepky [4] discussed the design, theory and principles of fluid bed granulators, such as mixing, agglomeration, drying, sieving of the granules, granulation time, reproducibility and scaling up. Kristensen and Schaefer [5] have identified the fundamentals of granule growth that are affected by changes on the methods of granulation and equipment (fluid bed and high shear mixers). In a fluid bed granulation, the spreading of the binder liquid droplet in the powder bed is critical, because it is this phenomenon that controls most of the agglomeration. Droplet size of the binder solution contacting the powder bed and humidity in

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the bed are key parameters. If one manages to understand the coalescence and growth process for the wet granules in terms of process variables upon optimization of the process, it will be possible to predict the end point properties of the wet granulation based on a numerical approach using a mechanistic modeling (population balance) of the process of granulation [6,7]. Boerefijn and Hounslow [1], managed to identify and quantify the dominant mechanisms found in the balance of fluxes of solids and binder, together with heat-transfer and conduction. The understanding of the mechanisms involved in granulation allows for the control of the growth kinetics and ease on scale-up procedures. However, the complexity of fluid bed granulation remains to be interily solved, and other approaches based on chemometrics and statistical analysis still play an important role on process understanding.

Scaling up encompasses the use of conservation equations to understand the process of agglomeration because the mass of the starting powder is conserved [6] together with the use of dimensionless numbers, independent of the scale considered (e.g. Froude, Reynolds, Power) that ultimately allows the identification of equations promoting a relationship between a set of dependent variables (the properties of the granules) and the independent variables (the processing and formulation components). By opposition to a complete empirical approach, multivariate statistics and chemometrics, on the other hand, can play an important role on scaling up a process. For instance, Faure et al. [2] have described several techniques, namely by monitoring one parameter and relating it backwards to one or more properties, modeling the process using experimental designs (once established, the models that can estimate the quality of the granules produced) or modeling the granule's population balance that require assumptions on the granulation. It follows that to extract the maximum information from the process of scaling up, different experimental designs [8] have been considered upon addressing this type of problems, namely, response surface methodology [9], factorial and multifactorial analysis, factor discriminant analysis, regression models [10]. Some authors [11,12] recognize that by employing models and simulations in identifying key transformations, linkages between process parameters and the material properties are reconciled in the form of controlling groups.

In a previous work, Dias and Pinto [13] have identified the most relevant factors that affect the production of granules in a laboratory scale fluid bed granulator. However, from an industrial perspective, it is important to identify changes on the properties of the granules in a process of scaling up.

This work suggests a different approach on the evaluation of the properties of granules produced in a laboratory and pilot scales granulators by the construction of a quality index based on a file of attributes. These attributes are combined by a methodology relying on Correspondence Analysis, as a discriminant procedure, using two extreme simulated active vectors [14].

2. Statistical analysis (methodology for the 'Granules Quality Index', GQI, construction)

The method considered to create a Granules Quality Index (GQI) is based on a multivariate statistical approach. The procedure involves three important steps, namely: (1) selection of the parameters to be included in the index; (2) standardization of the parameters and (3) the aggregation of the parameters. The type and number of parameters selected depends mainly on the purpose of the index construction and the availability of data.

In the present case, the GQI is created to monitor the impact of producing granules with laboratorial and pilot scale equipments on the quality of the granules.

The aggregation of the standardized parameters was developed by Benzécri in the early seventies [15]: the factorial correspondence analysis (FCA) belongs to a group of factor extraction methods whose main objective is to discover the underlying pattern of relationships within a data set. This is basically done by rearranging the data into a smaller number of uncorrelated "components" or "factors" that are extracted from the data by statistical transformations. Such transformations involve the diagonalization of the same sort of similarity matrix of the variables, such as a correlation or variance–covariance matrix. Each factor describes a certain amount of the statistical variance of the analyzed data and is interpreted according to the intercorrelated variables. The main advantage of FCA is that symmetry is conferred to the data matrix [14], thus allowing the simultaneous study of correlations within and between variables and samples. A detailed discussion of the theory behind FCA goes beyond the scope of this article, but its application in the present case is rather straightforward.

Experiments were run in triplicate according to a center of gravity design [16]. The formulation and processing conditions considered and the full experimental design are presented in Table 1.

As described earlier, the statistical technique considered subdivides each variable into three classes [14] as exemplified in Table 2. As an example, for variables *'PER2'*, the 1st class considered the results between 0% and 1%, the 2nd class, the results between 1% and 2% and the 3rd class, the results higher than 2% to the expected

Table 1
Design of the experiments according to the center of gravity design.

Number of experiment	Solubility of the drug (gl^{-1})	MW of PVP[a]	Ethanol (%)	Granulation solution rate (ml min^{-1})[c]	Atomizing air pressure (bar)	Inlet air temperature (°C)	Inlet air rate (m^3 h^{-1})[c]
1	0.00242	25	50	15/60	2	40	10/400
2[b]	**17**	**25**	**50**	15/60	**2**	**40**	10/400
3	260	25	50	15/60	2	40	10/400
4	17	17	50	15/60	2	40	10/400
5	17	30	50	15/60	2	40	10/400
6	17	25	20	15/60	2	40	10/400
7	17	25	80	15/60	2	40	10/400
8	17	25	50	10/40	2	40	10/400
9	17	25	50	20/75	2	40	10/400
10	17	25	50	15/60	0.5	40	10/400
11	17	25	50	15/60	4	40	10/400
12	17	25	50	15/60	2	30	10/400
13	17	25	50	15/60	2	50	10/400
14	17	25	50	15/60	2	40	5/200
15	17	25	50	15/60	2	40	15/600

[a] Average molecular weight of the polyvinylpyrrolidone chain.
[b] Center of gravity experiment.
[c] Values for the laboratory and pilot scale units, respectively.

Table 2
Example of standardization procedure used for building the GQI.

Case	PER2 (%)			Assay (%)			SIZ (μm)		
Classes	0 < (%) < 1	1 < (%) < 2	(%) > 2	99 < (%) < 102	95 < (%) < 99	(%) < 95	SIZ > 600	250 > SIZ > 600	SIZ < 250
GOOD (1)									
BAD (−1)									

result. Similarly, the *'assay'* and the *'siz'* (Table 2) and the remaining variables were also grouped into three classes.

Standardization of the variables occurs by applying a simply binary codification system to the samples: '0' if sample does not belong to class, '1' if it does. Aggregation of the standardized parameters into the final index value is performed by using a multivariate statistical approach based on the principle of factor correspondence analysis (FCA). Developed by Benzécri in the early sixties [15], FCA belongs to a group of factor extraction methods whose main objective is to discover the underlying pattern of relationships within a data set. This is basically done by rearranging the data into a small number of uncorrelated "components" or "factors" that are extracted from the data by statistical transformations. Such transformations involve the diagonalization of the same sort of similarity matrix of the variables, such as a correlation or variance–covariance matrix [17]. Each factor describes a certain amount of the statistical variance of the analyzed data and is interpreted according to the intercorrelated variables. The main advantage of FCA is that symmetry is conferred to the data matrix [17], thus permitting the simultaneous study of correlations within and between variables and samples.

A detailed discussion of the theory behind FCA goes beyond the scope of this article, but its application in the present case is rather straightforward. The first step involved the definition of two standard granules samples; one of very high and the other of very low quality (Table 2). The high-quality standard sample (the 'good' pole) has ideal values, whereas for the low-quality sample (the 'bad' pole), values considered doubled the ones for the high-quality standard sample. Following this procedure, each experimental sample result is located in an arbitrary scale defined by these two extreme poles, by the bias of the FCA supplementary projection. The resulting scores correspond to the final index values, which range between '−1' and '1' [15].

3. Materials and methods

3.1. Materials

Drug substances (Table 3) were supplied by Delta Laboratories (Portugal). The excipients considered were lactose monohydrate EP, 200 mesh (Meggle, Germany), polyvinylpyrrolidone of different grades (Kollidon 120 mesh K17PF, K25 and K30, BASF, Germany). Ethanol and freshly demineralized water were used in different proportions for the preparation of the solution of granulation.

3.2. Preparation of the granules in the laboratory and pilot scale granulation units

A standard formulation containing 1:8:1 parts of drug, lactose and polyvinylpyrrolidone was dissolved in a mixture of ethanol and water up to 3.85 parts. The alcoholic solution was prepared before the polyvinylpyrrolidone was added under stirring. Different formulations were prepared according to the experimental design presented in Table 4. Granules were prepared in fluidized bed granulators (UniGlatt and GPCG 15, Glatt Air Techniques, GmbH, Germany) in batches of 1 and 10 kg, respectively. The drug and lactose were mixed for 5 min. Then, granulation started by spraying the granulating solution over the powder for 60 min. Both mixing and granulation were carried out at an inlet air temperature of 40 °C. Granules were dried at 60 °C for 10 min. A typical process chart is shown in Figs. 1 and 2.

Table 3
Properties of the drugs used in the experiments.

Drug	Solubility in water at 21 °C (g l^{-1})	Molecular weight	Melting range (°C)
A	0.00242	1076.6	
B	17	170.3	131–133
C	260	179.2	195–196

3.3. Characterization of the granules

The yield of the process was found as the percentage of material collected from the container (*PER1*). Furthermore, to characterize the process, the percentage of granules over 2000 μm diameter (sieving) was determined as an indicator of a non controllable process (*PER2*). Further characterization of the granule's size was done by sieving 100 g of granules of each batch through a set of sieves in a $\sqrt{2}$ progression (Retsch, Germany), for 5 min. A cumulative percentage undersize plot was constructed and the median (*SIZ*) and the interquartile range (*IQR*) were determined. The friability of the granules was determined in an Roche type friabilator (T.A.3, Erweka, Germany) at 25 r.p.m. for 5 min, as described by Saleh and Stamm [18] *(FRI)*. The true density was determined by helium pycnometry (Micromeritics Accupyc 1330, USA) *(TD)*, whereas the bulk *(BD)* and tapped (*TaD*) densities were determined

Table 4
Formulation, processing conditions and levels of the variables considered in the experiments.

Independent variable		Level in the experiments[a]		
Solubility of the drug	SOL (g l^{-1})	0.00242	**17**	260
Average molecular weight of PVP	PVP	17	**25**	30
Granulation solution	GS (% of ethanol)	20	**50**	80
Granulation solution rate[b]	GR (mL min^{-1})	10/40	**15/60**	20/75
Atomizing air pressure	AP (bar)	0.5	**2**	4
Inlet air temperature	IAT (°C)	30	**40**	50
Inlet air rate[b]	IAR (m^3 h^{-1})	5/200	**10/400**	15/600

[a] Bold characters represent the values for the center of gravity in the experimental design.
[b] Values for the laboratory and pilot scale units, respectively.

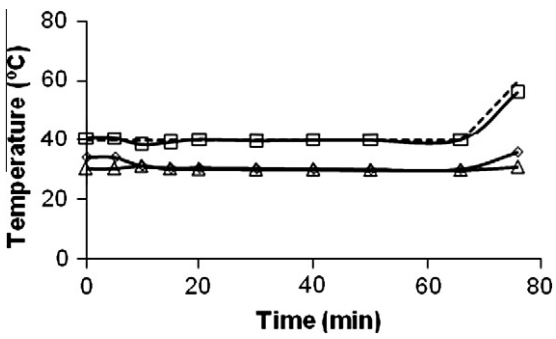


Fig. 1. Variation of the temperature throughout the process.

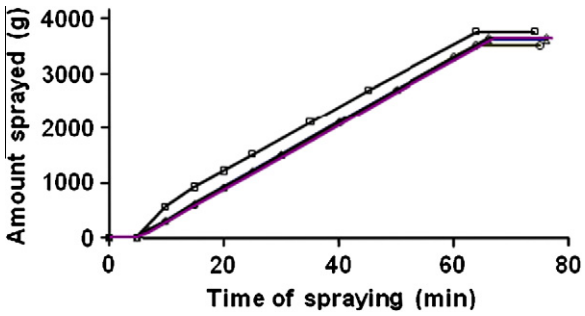


Fig. 2. Variation of the amount of granulation rate sprayed over time for different experiments (chosen randomly). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
Variables considered as properties of the granules.

Percentage of total granules produced	PER 1 (%)
Percentage of granules over 2000 μm diameter	PER 2 (%)
Drug assay	(%)
Median granule size	SIZ (μm)
Interquartile range	IQR (μm)
True density	TD (g cm^{-3})
Bulk density	BD (g cm^{-3}
Tapped density	TaD (g cm^{-3})
Carr's index	Carr
Angle of repose	AnRep
Flowability	FLO (g s^{-1})
Friability	FRI (%)

according to the European Pharmacopoeia [19] using a 250 mL measuring cylinder. In order to check a proper drug distribution within the batches, assays *(Assay)* of each drug in the granules were carried out. Drugs 'A' and 'C' were quantified by spectrophotometry (Perkin-Elmer spectrophotometer, 550 SE, USA), whereas drug 'B' was determined by potentiometry (Metron potentiometer, Herisau E 576, Switzerland). The flowability of the granules was assessed according to the method described in the European Pharmacopoeia (funnel) [19]. The Carr's index *(CARR)* was derived from the experimental values produced by the tests described previously (Table 5).

3.4. Statistical analysis – GQI construction

After all the variables classified in a set of classes and recoded the values of each experiment in a complete disjunctive table, a new framework, in which the column represents the different classes of variables (attributes) and lines represents experiments performed, the FCA is performed and the GQI obtained for each experiment (Table 6).

The experimental data were grouped in four classes, of equal range, allowing the representation of two extreme classes (best and worse results – extreme visualization) and two intermediary classes (central tendencies visualization). Assuming that the values for the index ranged between −1 and 1, the zero was assumed as the origin of the referential for the quality distribution of the data.

The original codification of the FCA was modified to achieve the objectives of this work, which are not limited to structural description of a framework of values, but needs a discriminant function that takes advantage of the projection on the virtual vectors ('Good' and 'Bad' vectors) of the experimental obtained vectors, allowing contribution of different weights, dynamically adjustable to each attribute.

4. Results

Table 7 summarizes the results (means) of the experiments carried out according to the experimental design in the laboratory scale equipment (Table 7, upper part) and the pilot scale equipment (Table 7, lower part). A fine analysis of the results did not show relevant changes within the same equipment or between equipments.

For a better understanding of the results, data were organized in order to analyze its distribution, namely the presence of asymmetries or/and the existence of outliers. The groups will illustrate possible bias introduced by the experimental procedures. The four classes of equal ranges chosen (Figs. 3–5) allow the visualization of the extremes and central tendencies behavior of the results emphasizing the relevant information. By doing so, possible bias introduced by the experimental procedures was minimized.

5. Discussion

The construction of the quality index – GQI – allowed the construction of a synthetic new variable. As a consequence, it was possible to analyze the results identifying patterns between the equipments and also between the different experiments carried out in the same equipment. The multivariate technique, by considering all data simultaneously, enabled the identification of patterns between the equipments, thus providing a full understanding of the work in opposition to the traditional approach of analyzing the results considering variable by variable.

Table 6
Example of the GQI index obtained to a set of experiments: the disjunctive table.

GQI Index	Case	PER1 (%) 95–100	PER1 (%) 90–95	PER2 (%) < 1	PER2 (%) 1–2	PER2 (%) > 2	Assay (%) 99–102	Assay (%) 95–99	Assay (%) < 95	SIZ (mm) > 600	SIZ (mm) 250–600	SIZ (mm) < 250
0.005	1	1.000	0.000	0.990	0.005	0.005	0.000	1.000	0.000	1.000	0.000	0.990
−0.099	**2**	1.000	0.000	0.990	0.005	0.005	0.000	1.000	0.000	1.000	0.000	0.990
0.104	3	1.000	0.000	0.990	0.005	0.005	0.000	1.000	0.000	1.000	0.000	0.990
0.104	4	1.000	0.000	0.000	1.000	0.000	0.990	0.005	0.005	1.000	0.000	0.000
0.505	5	1.000	0.000	0.000	1.000	0.000	0.990	0.005	0.005	1.000	0.000	0.000
0.505	6	1.000	0.000	0.000	1.000	0.000	0.990	0.005	0.005	1.000	0.000	0.000
0.099	7	1.000	0.000	0.990	0.005	0.005	0.990	0.005	0.005	1.000	0.000	0.990
−0.198	8	1.000	0.000	0.990	0.005	0.005	0.990	0.005	0.005	1.000	0.000	0.990
0.208	9	1.000	0.000	0.990	0.005	0.005	0.990	0.005	0.005	1.000	0.000	0.990
−0.198	10	0.000	1.000	0.000	1.000	0.000	0.000	1.000	0.000	0.000	1.000	0.000
0.104	11	0.000	1.000	0.000	1.000	0.000	0.000	1.000	0.000	0.000	1.000	0.000
0.005	12	0.000	1.000	0.000	1.000	0.000	0.000	1.000	0.000	0.000	1.000	0.000
−0.198	13	1.000	0.000	0.990	0.005	0.005	0.990	0.005	0.005	1.000	0.000	0.990
0.401	14	1.000	0.000	0.990	0.005	0.005	0.990	0.005	0.005	1.000	0.000	0.990
0.198	15	1.000	0.000	0.990	0.005	0.005	0.990	0.005	0.005	1.000	0.000	0.990

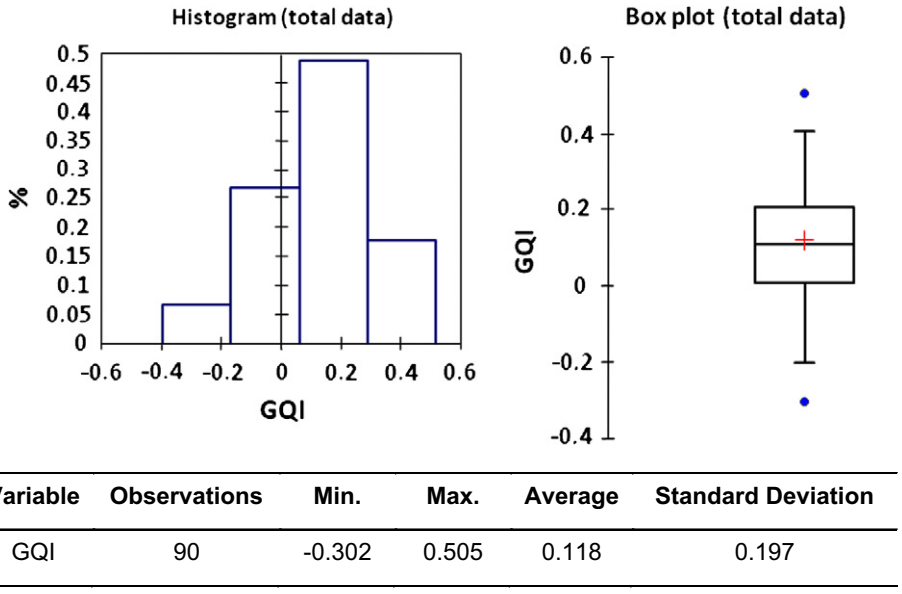
Good vector – (1); Bad vector – (−1)

Table 7
Properties of the granules (upper table – laboratory scale; lower table – pilot scale).

Case #	Yield (%)	Large gran. (%)	Assay (%)	Size (μm)	IQR (μm)	True density (g cm^{-3})	Bulk density (g cm^{-3})	Tap density (g cm^{-3})	Carr's index	FLO (g s^{-1})	FRI (%)
1	95.1	0.7	97.4	280.0	57.5	1.47	0.39	0.43	7.8	0.3	5.6
2[a]	97.9	1.1	99.6	380.0	59.6	1.45	0.39	0.42	7.7	0.3	1.9
3	95.6	0.9	101.2	505.0	56.1	1.48	0.40	0.44	9.3	0.3	0.5
4	94.5	2.2	98.9	300.0	66.8	1.45	0.43	0.48	9.7	0.4	5.6
5	95.4	1.1	98.4	390.0	52.4	1.46	0.39	0.43	9.5	0.4	2.3
6	92.5	1.7	98.4	655.0	67.6	1.46	0.50	0.57	12.5	0.3	0.1
7	98.8	0.7	101.4	475.0	52.0	1.46	0.47	0.43	8.9	0.3	4.1
8	97.0	1.8	99.1	430.0	54.8	1.46	0.39	0.44	9.6	0.4	3.6
9	94.5	3.4	97.5	501.7	56.8	1.45	0.40	0.56	11.1	0.3	0.6
10	90.5	1.2	98.8	985.0	61.2	1.46	0.39	0.48	8.8	0.3	0.3
11	97.3	25.9	100.6	440.0	59.2	1.45	0.38	0.44	11.5	0.3	3.5
12	93.5	1.4	98.8	410.0	63.5	1.45	0.45	0.54	9.8	0.3	1.1
13	95.6	0.9	100.2	400.0	51.2	1.45	0.42	0.42	8.7	0.3	2.9
14	94.0	1.3	98.3	370.0	68.2	1.46	0.45	0.50	10.1	0.3	2.6
15	95.2	1.4	89.9	801.7	56.8	1.45	0.45	0.49	7.9	0.3	1.0

Case #	Yield (%)	Large gran. (%)	Assay (%)	Size (μm)	IQR (μm)	True density (g cm^{-3})	Bulk density (g cm^{-3})	Tap density (g cm^{-3})	Carr's index	Angle repo	FLO (g s^{-1})	FRI (%)
1	98.2	0.01	95.7	135.5	84.0	1.53	0.37	0.49	24.1	43.1	3.58	26.8
2[a]	99.0	0.04	96.3	168.5	107.7	1.48	0.35	0.47	23.6	40.0	4.72	13.4
3	99.0	0.04	92.9	131.6	76.5	1.47	0.36	0.47	24.6	39.3	3.71	23.2
4	95.9	0.01	107.3	139.4	87.5	1.48	0.38	0.49	23.6	39.8	4.46	16.2
5	102.3	0.07	100.5	189.7	121.7	1.48	0.34	0.44	23.9	40.1	5.14	10.2
6	99.0	2.10	103.1	134.4	184.2	1.45	0.54	0.73	24.1	45.1	3.25	6.7
7	100.7	0.02	96.1	202.9	124.5	1.46	0.34	0.45	18.9	41.7	4.64	12.4
8	97.7	2.36	113.5	303.1	453.6	1.46	0.53	0.65	18.0	45.0	6.92	3.7
9	99.7	0.03	110.0	111.9	95.9	1.48	0.49	0.65	21.2	40.2	3.80	21.9
10	101.6	0.04	91.8	189.5	121.6	1.47	0.34	0.45	24.1	40.7	4.90	12.4
11	99.7	0.09	104.8	94.9	159.8	1.47	0.48	0.66	25.9	45.9	3.68	22.5
12	98.2	0.01	95.7	135.5	84.0	1.52	0.37	0.49	24.1	43.1	3.58	26.8
13	99.0	0.04	96.3	168.5	107.7	1.48	0.35	0.47	23.6	40.0	4.72	13.4
14	99.0	0.04	92.9	131.6	76.5	1.47	0.36	0.47	24.6	39.3	3.71	23.2
15	95.9	0.01	107.3	139.4	87.5	1.48	0.38	0.49	23.6	39.8	4.46	16.2

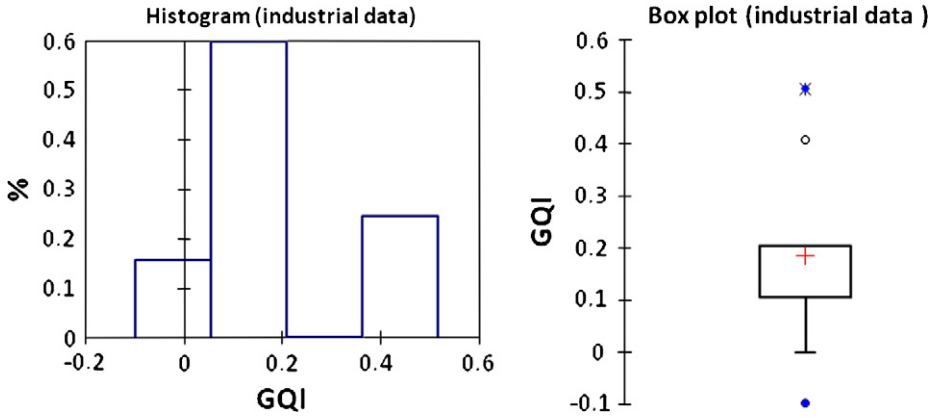
[a] Center of gravity experiment.



Variable	Observations	Min.	Max.	Average	Standard Deviation
GQI	90	-0.302	0.505	0.118	0.197

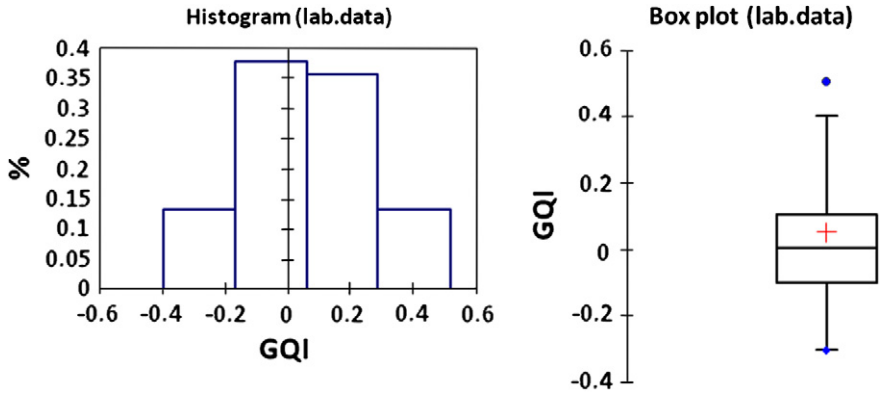
Fig. 3. GQI distribution – pilot and laboratory scale. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In Fig. 3, the total data distribution can be seen, whereas in Figs. 4 and 5, one can observe separately the granules produced by the pilot scale and laboratorial equipments, respectively. Thus, the overall distribution of the GQI is characterized emphasizing the contributions of the pilot scale equipment versus the laboratory scale one. It is also necessary to understand if the quality of the process (in the present case, the wet granulation) (reflected on high values of the GQI) is homogeneously distributed (Fig. 3, left) or, if there are tests that generate extreme values (reflected by maximum or minimum values for the GQI) (Fig. 3, right). In the present situation, the process is generally well controlled although some results can be regarded as outliers. It follows that the correct evaluation of the causes of extreme values from the process is, from the standpoint of quality control, very important because it



Variable	Observations	Min.	Max.	Average	Standard Deviation
GQI	45	-0.099	0.505	0.190	0.190

Fig. 4. GQI distribution – pilot scale. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Variable	Observations	Min.	Max.	Average	Standard Deviation
GQI	45	-0.302	0.505	0.052	0.184

Fig. 5. GQI distribution – laboratory scale. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

may reflect a deficient operational implementation. In fact, the synthetic variable allowed the perception of the existence of outliers that the analysis of each and all variables did not show.

Observing the histogram presented in Fig. 4 (left) (GQI for the experiments run in a pilot scale equipment), it is possible to see a clear difference between the pattern for the distribution of data. Furthermore, the data produced by this equipment show a distribution with and apparent strong asymmetry on the right, by opposition to the data produced from the laboratory scale equipment (Fig. 5, left), which presents an almost symmetrical distribution. This observation is further explained by the observation of its box plot representation (Fig. 4, right), where extreme values (marked by the dots) appear promoting the asymmetry observed in the histogram (Fig. 4, left). The results have shown that at the pilot scale, outliers were generated strongly suggesting that a better control of the process is required, namely by increasing the controls on the process and on the granules under production. The data produced by the laboratory scale equipment were more homogeneous, where the box plot representations confirm the symmetry of the distribution histogram (Fig. 5, right and left), thus the process was under control and the tests considered for the characterization of the granules were sufficient.

It should be noted that two main observations must be referred. The results obtained with the pilot scale equipment are in frequency of better quality (*i.e.* higher values for the central classes) when compared to the ones produced by the laboratory scale equipment (*i.e.,* lower values). The extreme values distribution is, however, more favorable when we analyze the laboratory scale data. Although the pilot scale process has shown higher frequencies, one should be aware of possible bias introduced in the process of granulation when processing the materials at this scale. In fact, two results from the pilot scale equipments were severely anomalous with extreme positive values, experiments that by not anticipated reasons produced anomalous results, eventually due to experimental conditions inadequate for the product and/or equipment, consequently, the production in the pilot scale equipment requires a more critical approach than the production at laboratory scale equipment.

6. Conclusions

The study has emphasized the complexity of a process of granulation whereby two different scale equipments processed the raw materials differently, as reflected by the different properties of the granules produced.

The statistical methodology considered has the advantage of showing the full picture of the process. However, it must be pointed out that variables do have different degrees of importance that were not considered in the study. It means that a careful planning of the experiments and future analysis of the variables considered are of paramount importance.

The study has emphasized the good scalability of both equipments by considering equivalents the results, once the outliers are excluded. This is critical for a company willing to carry out a process of scaling up of a new medicine.

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