International
OPEN ACCESS Journal
Of Modern Engineering Research (IJMER)

Evaluation of The Inter-Batch Variability of An Active Pharmaceutical Ingredient: Morphologic, Rheologic And Calorimetric Characterization

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ABSTRACT:*All raw materials used for solid oral drugs manufacturing must be evaluated according to the pharmacopoeial monographs, which consist in a verification of critical quality attributes related to the identity and purity of the molecule. However, active pharmaceutical ingredients may present differences in non-pharmacopoeial tests, such as particle size and shape or flow. Although these differences are not evaluated routinely by Quality Control area, they can alter the technological performance during production, as well the stability and ultimately the efficacy of a pharmaceutical product. In this study, 10 production batches of magnesium valproate were evaluated, characterizing flow index, fusion enthalpy and particle shape and size distribution. An analysis of variance was carried out, finding statistically-significant differences in the flow index, particle shape and fusion enthalpy tests for two batches. These differences may be due to small variations in the crystalline configurations. The study showed differences in the characterization of fundamental and functional properties of the particles of the active pharmaceutical ingredient evaluated, which could have an impact on the manufacturing processes and affect therapeutic efficacy.*

KEY WORDS:*Solid characterization, Batch-to-batch variation, Particle shape, Powder flow tester,*

Date of Submission: 03-10-2018 Date of acceptance: 15-10-2018

I. INTRODUCTION

Within the pharmaceutical industry, the raw materials used in the manufacture of solid oral drugs (SOD) must be evaluated according to pharmacopoeial monographs. These monographs precisely consist in the verification of critical quality attributes (CQA) related mostly to the identity and purity of the molecules that were established in phases prior to commercialization of the product. However, the excipients and active pharmaceutical ingredients (API) may present differences in non-pharmacopoeial tests that are not routinely evaluated by the Quality Control (QC) department, such as the crystallographic characterization or the particle size distribution (PSD) and shape. These non-pharmacopoeial attributes should be considered when establishing a Target Product Profile (TPP). Shekunov and collaborators sustain that the effects of particle size and shape, purity and structural defects, followed by less-pronounced but significant variations in the thermodynamic and mechanical properties, are the main source of the problems of batch-to-batch variation and inconsistency in the properties of tablets [1]. Buckton assures that the energy of the manufacturing process and the manner and capacity of the materials to recover from the tension produced by this energy affects batch-to-batch uniformity [2]. Differences between suppliers or batches from the same supplier that are not detectable by

pharmacopoeialmethods could somewhat alter the technological performance during manufacture of SOD, as well as the stability and ultimately the efficacy and safety of the pharmaceutical products.

Crystallization, a technique widely used in the fabrication and purification of active ingredients obtained by organic synthesis reactions, defines the chemical purity of the drug and its physical properties such as structural and crystal habit, degree of crystallinity and particle size [1]. The conditions in which this technique is carried out (temperature, cooling speed, presence of impurities and type of solvent used, for example) affect fundamental properties of the solid state exhibited by the final product, such as morphology, size and particle shape, surface area, porosity and density [3]. The improvements in the high scale pharmochemical manufacturing processes make possible to obtain a controlled identity and high purity of a molecule, but the control of the degree of crystallinity and the shape of the particles produced continues to be a challenge [1]. Also, the absence of specifications related to the fundamental properties of the particles by the manufacturers of the final pharmaceutical form leads to pharmacochemical companies not establishing finer production controls for these quality attributes. Even the slightest changes in the conditions of crystallization can lead to significant changes in the properties of the particulate matter (namely powders) [2]. Different crystalline forms of a drug differ in their specific surface and surface free energy [4], which may present variations in hygroscopicity, solubility [5], dissolution speed [6-9], flow properties [10], compression profile [7, 11, 12], biopharmaceutical parameters and physical and chemical stability [1, 11, 13-18].

The presence of different habits is defined, in great measure, by external factors (solvent, temperature, supersaturation and impurities) during crystallization, being a consequence of the growth rate on the faces of the crystal [19]. Thus, some drugs can present crystals that are different in their macroscopic appearance but not in a molecular arrangement level; in other words, they may present different habits, without having differences in their inner crystalline network. These forms are known as isomorphs [20, 21]. Isomorphs can deploy differences in their physicochemical properties due to the arrangement or orientation of the functional groups during crystallization. These variations may affect the functional properties of the particles, such as the flow function [22, 23], flow speed, resistance to rupture [4], compressibility [7, 24], as well as the dissolution behavior [25, 26]. Besides changes in the mechanical or technological behavior of the active ingredient in a pharmaceutical form, the crystal habit can influence the intrinsic dissolution speed, be it through modifications induced by the conditions of the crystallization process [27], the presence of polymorphs [9, 14, 26, 28-31] or by means of modifications that lead to the appearance of the amorphous phase of a crystalline solid [13, 15]. The intrinsic dissolution of celecoxib, for example, changes according to the crystalline form being evaluated; better intrinsic dissolution speeds of the habits were found in plate shaped particles [25]. Other effects of the crystal habit have been reported in densification and compressibility properties for ibuprofen [7].

The surface energy of a crystalline powder is directly related to the functional groups exposed on the face of the crystal; an unequal surface energy of the crystalline powders could have an impact on the cohesion of the powder [32]. Particle morphology and size distribution also have consequences over the physical properties of the manufacturing process and the quality attributes of the SOD. Both influence pharmacokinetic parameters such as dissolution rate [33, 34], distribution and in vivo deposition of the particles. These two properties may also alter tests results for titration, content uniformity and flow, among others [18, 34]. In tablet manufacturing [35], for example, particle shape and size affect almost any stage of the process, from mixing [36], granulation [37] and compression [36] to coating [18, 38], all of which affect the dissolution [39] and stability [40] of these tablets and coated tablets.

Magnesium valproate (VaMg) is a broad-spectrum, anti-convulsive drug; in other words, it has an effect over both generalized and partial convulsions. It is indicated in the treatment of epilepsy, mania and migraine [41]. This molecule is the magnesium salt of valproic acid; the therapeutic effects that produces are the result of the combination of the valproic acid with the magnesium ion (so they act in a complementary way). It is considered that VaMg increases the concentration of γaminobutiric acid (GABA), rising up the conductivity of Cl^- and K^+ ions and reducing the stimulation of the N-methyl-D-aspartate receptor (NMDA). The Mg^{2+} ion reduces the conductivity of Ca^{2+}, activates the Na^+/K^+ ion pump and modulates the NMDA receptors of the neuronal membrane. It is also reported that valproate exerts different effects over neurotransmitters [42, 43].

After its administration, VaMg is hydrolyzed into magnesium ions and valproic acid, having a biological half-life of 8 to 16 hours. It is mainly metabolized in the liver. Only 3% is eliminated through urine. Table I summarizes the pharmacokinetic data of this API [41].

Table I: Pharmacokinetic parameters of magnesium valproate, obtained from 108 mg/kg of VaMg, equivalent to 100 mg/kg of valproic acid [41]

Pharmacokinetics parameters	Value	Physicochemical characteristics	Value
Half-life	6.97 h average (8 to 16 h)	Solubility in water	1.3 mg/mL
Distribution volume	1.5 L/kg	Solubility in organic solvents	Highly soluble
Clearance	0.49 mL/min	Log P	2.75
AUC	596.6 mg/mL/h	pKa	4.8
C_{max}	57.2 (mg/mL)	Refraction index	1.425-24.5
T_{max}	1 h		

As a drug, VaMg is commercialized in various liquid and solid pharmaceutical forms. The SOD presentations are available in doses of 200, 300, 400, 500 and 600 mg per tablet, either with an enteric coating or a prolonged release core. Among manufacturers VaMg hay a poor flow reputation. With regard to medium and high VaMg doses per tablet and its limited fluidity, we selected it as a model API for this study. In this work, it is demonstrated that inter-batch API variations exist related to the solid state of this anti-convulsive pharmaceutical, which are not detectable by the quality analysis required by the pharmacopoeias; these variations could alter the technological performance of the pharmaceutical during the production process. Hypothetically, this differences could modify the safety and therapeutic efficacy of solid oral drugs.

II. MATERIAL AND METHODS

Materials

Ten batches of VaMg were used, provided by the same manufacturer (not declared due to a confidentiality agreement), which were consecutively numbered from 1 to 10. All the batches were approved with the same quality specifications.

Methods

An experimental, comparative and prospective study was carried out. The experimental design was unifactorial, with 10 levels, measuring the following output data:

1. **Flow function**: Samples (n=2) were evaluated in a Brookfield Powder Flow Tester (PFT) shear cell using a vane lid cell and a Precisa ES 4200 scale. Flow values were obtained, expressed as the slope of the line resulting from plotting the unconfined failure stress (kPa) vs. principal consolidation stress (kPa). The Brookfield annular cutting cell equipment complies with the requirements of the "D6128: Standard Test Method for Shear Testing of Bulk Solids Using theJenike Shear Tester" of the American Society of Testing Materials (ASTM) [44-46]. The flow function curve (ff_c) gives a measure of the amount of strength the material retains at a stress free surface following consolidation to a given stress level, thus calculating the force necessary within the cell to achieve the sample flow. This resistance or relative fluidity is represented by the flow index (FI), expressed as the relationship between the largest stress acting on the powder during steady state flow (major principal consolidation stress) and the stress required to cause a powder to flow at a stress free surface, after it has been compacted to a given consolidation level (unconfined failure strength); in other words, the FI is the inverse of the slope of the ff_c. Equation 1 describes the mathematical relationship between both forces involved in the flow function that is obtained in the PFT.

Equation 1

$$\mathrm{IF} = \frac{1}{\mathrm{ff_c}} \rightarrow \mathrm{ff_c} = \frac{\sigma_1}{\sigma_c} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

Where ff_c is the flow function, □ 1 is the major principal consolidation stress and σc is the unconfined failure strength.

2. **Fusion enthalpy:** The enthalpy of thermic events was measured through differential scanning calorimetry (DSC), in a Mettler-Toledo DSC3 equipped with a STAR software, using 5 mg samples (n=3), exactly weighed on a Mettler-Toledo XP6 microscale, sealed in 40 μL aluminum melting pots, with a heating rate of 3°C/min, under a nitrogen flow of 40 mL/min, with an indium standard (In), in a temperature interval of 70-160°C. DSC technique allows to calculate the change in enthalpy by the difference of temperature between the sample and reference. In endothermic processes (i.e. energy absorption processes, such as fusion or evaporation), the enthalpy of the system increases, while in exothermic processes (condensation, crystallization), the enthalpy and internal energy of the system decreases [47].

3. **Shape:** The particle morphology of the samples was analyzed in a Malvern Morphologi G3 using a 10x objective and an automated dispersion unit. UN 1002 grade-zero compressed air (Infra, batch 151220160208) was pumped at a 5 bar pressure and a running time of 120 minutes. Samples (n=2) were handled with a 3 mm3 spatula and augmented images of each particle were directly observed. With the image analysis software integrated to the equipment, the circularity (Ci) was determined. Ci is defined as the degree to which the particle is similar to a circle, considering the softness of the perimeter; therefore, it is a measure of the shape, as well as the roughness of the particle. This parameter is calculated using Equation 2.

Equation 2

$$\mathrm{Ci} = \sqrt{4\pi \mathrm{A}} / \mathrm{P}^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots.(3)$$

Where Ci=circularity, A = area of the particle and P = parameter of the particle. The more distant the shape is from a perfectly-round and smooth circle, the lesser the value of its circularity will be.

In order to evaluate the level of content (percentage) of each of the shapes detected, a software's "filter tool" was applied to the Ci parameter. An arbitrary cut in the value of Ci was established at a value of 0.75 or greater, in order to define the shape of the particle as a "plate". The rest of the particles were called "rods" for its visual similarity to this shape when observing them with the microscope.

4. **Particle Size Distribution (PSD):** A Malvern Morphologi G3 with a 10x objective, using the automated dispersion unit with a compressed air pressure of 5 bars and a running time of 120 minutes was employed. The samples (n=2) were handled with a 3 mm^3 spatula. The mean diameters D_{10}, D_{50} and D_{90} were determined.

5. **Data analysis:** For all of the samples, a one-way analysis of variance (ANOVA) was carried out, using the Statgraphics Centurion XV statistics package with a 95% confidence and a level of significance of 0.5%. In the event that significant differences were found, the Fisher LSD test was applied. The hypothesis proposed were:

H0: There are no significant differences between the levels of the factor
HA: There are significant differences between the levels of the factor

III. RESULTS AND DISCUSSIONS

1. **Flow function**: Four of the batches (number 1, 7, 9 and 10) presented significant differences ($p<0.0001$) in the FI value. These four batches also had FI values below 0.5, which means they present less resistance to failure within the shear cell and thus are categorized as "cohesive" powders by the software integrated to the PFT. The rest of the samples presented FI categorized as "very cohesive" powders. Table II shows the results of the FI values for the 10 batches. Figure 1 presents the flow profiles of all the batches assessed by this technique.

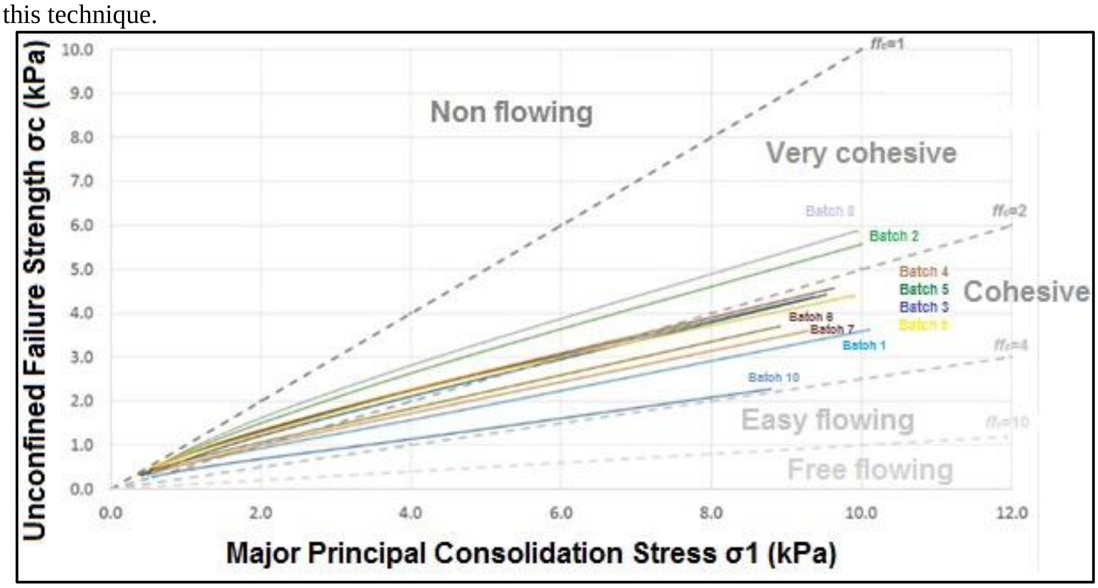

Figure 1. Flow function graph

2. **Fusion enthalpy:** Two thermic events were found in all the samples at approximately 120 °C and 144 °C, respectively. In Figure 3, the resulting thermograms for the 10 batches can be observed. Batches 1 and 10 presented significant differences (p=0.0001) in both thermic events, while the second event is also different for batch 6 (p‹0.0001). These batches present the lowest enthalpy values in both thermic events, as is shown in Table II.

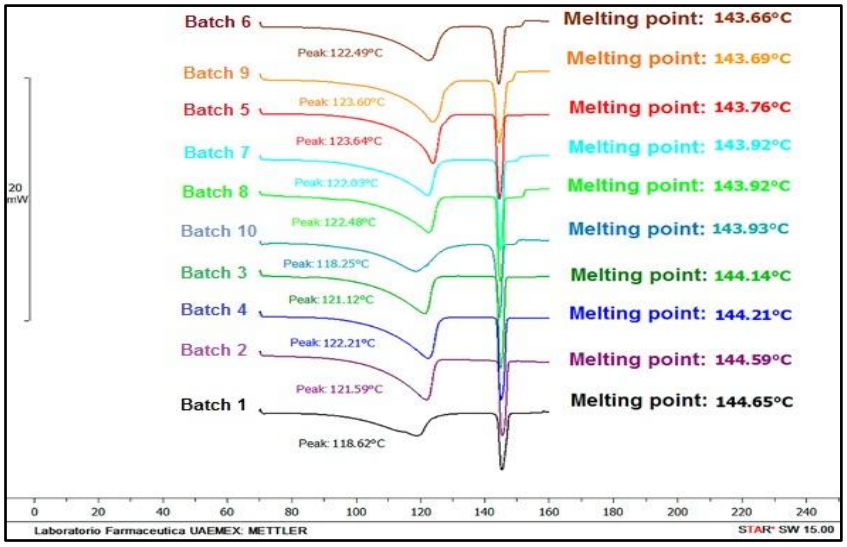

Figure 2. Thermograms for 10 VaMg batches

3. **Shape**: Two particle shapes were detected (plates and bars) in all the samples. The ANOVA for Ci shows that batches 1, 7, 9 and 10 have the shape closest to a circle (p=0.0006). The LSD test notifies of the existence of homogenous groups having different Ci values; batches 4 and 8, for example, have the most particles with an elongated shape. The quantitative morphologic analysis, expressed in terms of the proportion of particles detected with the shape of a plate, exhibits significant differences (p=0.0002) for batches 1, 7 and 10, which are the ones with the highest content of plate shaped particles. Another homogenous group, which is the one with the lowest plate content, consists of batches 4, 5 and 8. Figure 3 shows the qualitative morphologic results and Figure 4 shows the plot with the difference of means for the circularity parameter, where four groups can be seen; the highest values of Ci are in highlighted in fuchsia, and are also the ones that present the best behavior. In descending order of circularity and flow, we can see blue, green and yellow groups. Additionally Table II shows the quantitative values of Ci.

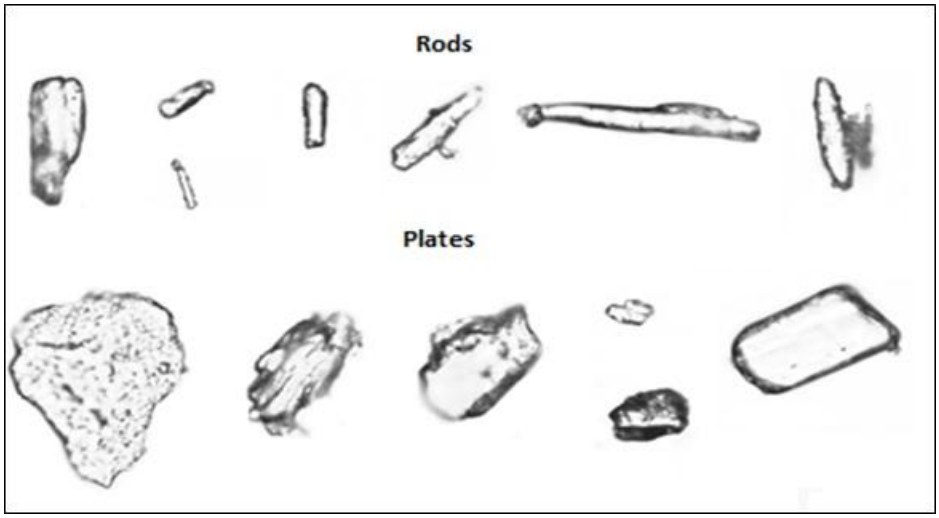

Figure 3. Shapes of the particles found in the batches evaluated

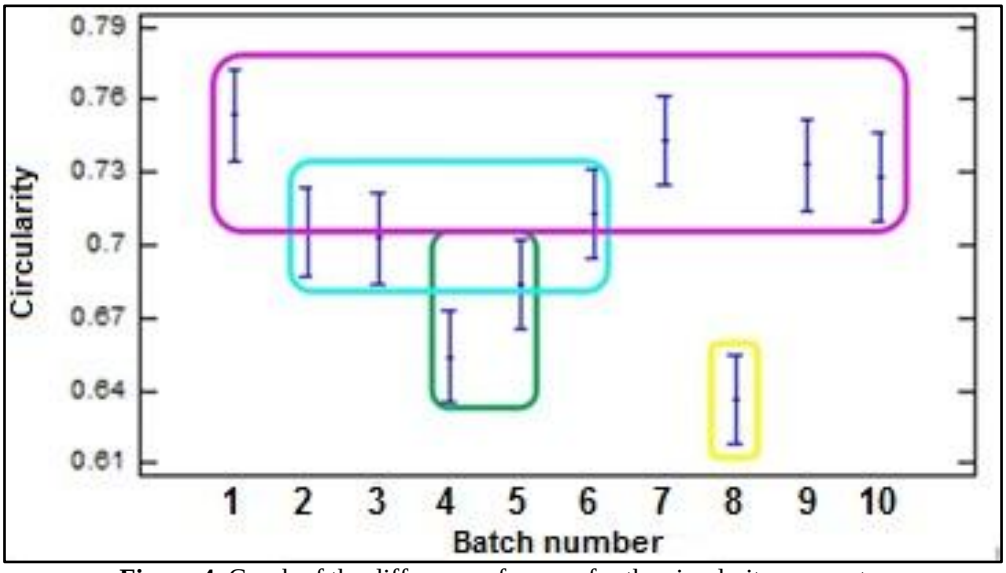

Figure 4. Graph of the difference of means for the circularity parameter

4. **PSD**: No significative differences were found in the mean diameter of the batches evaluated, related to D_{50} y D_{90} measurements. However, different homogenous groups were formed, which implies that there are batches with a greater proportion of thick particles. The group formed by batches 1, 5, 8 and 9 have the highest D_{50} values, while batches 1, 4, 5 and 8 show greater values of D_{90} (p=0.0495, p=0.0006, respectively). Table III shows the values of PSD.

Table II: Results of the evaluation of the active ingredient

Batch	Flow index		ff_c	Powder classification	Fusion enthalpy (J/g)		Enthalpy of first thermic event (J/g)		Circularity		% of plates	
	mean	SD			mean	SD	mean	SD	mean	SD	mean	SD
1	0.35	0.007	2.86	C	43.60	3.106	129.50	12.620	0.75	0.022	78.42	4.349
2	0.57	0.021	1.75	VC	50.44	0.590	160.09	4.910	0.71	0.013	67.57	2.814
3	0.55	0.028	1.81	VC	49.95	0.665	153.71	1.082	0.70	0.008	66.97	1.556
4	0.56	0.042	1.78	VC	49.85	0.595	161.97	1.373	0.65	0.028	58.89	4.038
5	0.56	0.049	1.78	VC	49.53	0.057	156.50	3.585	0.68	0.017	63.57	3.811
6	0.54	0.028	1.85	VC	45.78	1.998	149.88	6.341	0.71	0.003	69.42	0.665
7	0.39	0.000	2.56	C	50.76	0.413	150.33	3.808	0.74	0.020	75.23	4.462
8	0.60	0.014	1.66	VC	50.90	0.581	159.85	5.361	0.64	0.002	53.65	0.643
9	0.48	0.021	2.08	C	48.92	1.375	157.38	3.684	0.73	0.023	71.01	1.803
10	0.26	0.021	3.84	C	45.74	1.530	143.67	3.245	0.73	0.008	72.08	1.598

C: Cohesive, VC: Very cohesive, ff_c: Flow function, SD: Standard deviation, Underlined: Significant differences

Table III: Results of the evaluation of the active ingredient (PSD)

Batch	D_{10} (µm)		D_{50} (µm)		D_{90}(µm)		Mean diameter (µm)	
	mean	SD	mean	SD	mean	SD	mean	SD
1	1.89	0.177	5.81	0.359	12.14	0.735	6.70	0.431
2	1.56	0.042	4.27	0.177	9.03	0.000	5.06	0.212
3	1.43	0.000	3.59	0.092	8.68	0.262	4.59	0.021
4	1.54	0.113	4.46	0.544	11.39	0.962	5.77	0.530
5	1.72	0.000	5.25	0.163	11.35	0.509	6.17	0.226
6	1.54	0.247	4.06	1.146	9.77	1.676	5.23	1.117
7	1.49	0.078	3.77	0.474	9.41	0.658	4.98	0.431
8	1.69	0.021	5.44	0.035	12.33	0.021	6.50	0.035
9	1.91	0.410	5.01	1.054	10.08	1.739	5.72	1.117
10	1.43	0.191	3.42	0.877	8.51	2.065	4.66	1.167

SD: Standard deviation, Underlined: Significant differences

IV. DISCUSSION

According to Mockus and collaborators, the improvement in the quality of a process can be seen as the reduction of the variation to a reasonable degree [48]. Getting to know and measuring this variation is an important element in order to achieve a TPP and Quality by Design [49]. Due to the fact that the source of variation in a process can be given, among other factors, by the variation in the raw materials, it is necessary to know and determine its impact in the technological performance.

The evaluation of the FI was carried out through a shear cell. Though this method is described in the USP, its application is not mandatory to assess an API's quality, insomuch that it is not contemplated in the pharmacopoeial monographs for individual QC analysis [50]; however, since flow is the convergence of different physical and physicochemical properties of a solid, its evaluation can help demonstrate existing differences among several raw materials and products. The results show that batches 1, 7, 9 and 10 behave as "cohesive" powders, while the rest are the "very cohesive" powders. This is in accordance with the direct observation derived from the manipulation of the products: batches 1 and 10 presented greater ease of pouring than batches 7 and 9. These categories coincide with the study carried out by Liu and collaborators that indicates that flow reflects the resistance to particle agglomeration [51], since the batches classified as "very cohesive" presented a high tendency to form agglomerates during manipulation.

In general, it has been accepted that the increase in particle size improves flow, as is reported by Liu and collaborators for ibuprofen through both the Hausner index and the shear cell techniques [52]. In this study, significant differences were found in D_{50} and D_{90}, without finding a correlation between the increase in particle size and an improved flow index [53].

The crystal habit also has an influence in the technological development of the API. As can be observed in Figure 2, the calorimetric behavior of the API, the two thermic events found in the temperature interval of the test, can be indicative of different solid states which are found in different proportions, such as the presence of isomorphs [24]. When Buckovec and collaborators studied different crystal habits of simvastatin, they found that it was possible to alter the dissolution speed by only modifying the crystal habit, and that crystals with a "bar" form presented a plastic deformation which affected disintegration [26].

As can be seen in Figure 4, in the morphologic study two shapes of the particle were found, which were identified as "rods" and "plates", derived from the measurement of Ci. While carrying out a correlation study between the Ci parameter and the plate-shaped particle content with the FI, a positive correlation was found ($p=0.0163$ y $p=0.0030$, respectively), insomuch that the fastest flow indexes were found in batches 1, 7, 9 and 10, with the highest circularity values and the highest plate contents (›0.72 y ›70%, respectively). In this same manner, we observed that batch 9 had the lowest plate content and the poorest flow of all the batches. Also, it was observed that batches 1 and 10 presented both the lowest FI and enthalpy values (Table II).

With these results, the presence of inter-batch variations in the API is evident, which, according to that documented in bibliography, may generate lack of robustness in the formula. Because of this, it is necessary to establish non-pharmacopoeial critical quality parameters in the routine analyses of raw materials in order to guarantee the final quality of a drug [29, 54] and assure a given TPP. In this sense, it is of vital importance to carry out the characterization of raw materials at a deeper level, which allows for the comprehension of the inter-particle attributes, with techniques that help demonstrating the technological performance of these, since the pharmacopoeic monographs currently establish the use of tests that are related merely to identification and purity attributes of a chemical entity. Tests such as the flow index, particle size distribution and the particle morphology through automated image analysis are considered necessary for the evaluation of the raw materials. These would allow for the quality of drugs to be guaranteed with robust processes and safe and efficient drugs.

V. CONCLUSIONS AND RECOMMENDATIONS

1- The small variations within the manufacturing design space of an API may yield differences that would affect the technological performance of that raw material in the manufacture process of a SOD, despite complying with the mandatory analysis required for its release.

2- The compendial evaluation of an API is not enough to describe it as a pharmaceutical raw material. The characterization of the solid, which includes morphologic, calorimetric and rheological aspects, can aid in a better comprehension of the performance of the raw materials.

3- The use of API batch-to-batch performance tests (such as those evaluated in this work) can be a valuable tool in order to achieve a better control of the crystallization process.

4- The use of API batch-to-batch performance tests (such as those evaluated in this work) would provide consistency to the pharmaceutical processes of interest both for Research and Development and QC departments.

5- The impact of the batch-to-batch variations of the raw materials involved in a pharmaceutical fabrication process is an issue that could have repercussions in the quality of the final product and production costs.

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1Alcantara-Fierro Edna Teresa "Evaluation of The Inter-Batch Variability of An Active Pharmacuetical Ingredient: Morphologic, Rheologic And Calorimetric Characterization"International Journal Of Modern Engineering Research (IJMER), vol. 08, no.