Wet Granulation End-Point Determination of a Drug Formulation

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Abstract *— Wet granulation is commonly used in oral solid dosage industry. The end-point is required to design a process that consistently meet products Critical Quality Attributes (CQAs) and the Critical Processing Parameters (CPPs). There are many methods available for end-point determination with their owns constraints of reproductivity and accuracy. Torque measurer was installed on the Low shear granulation and product "XA" was monitored. The results confirm that automated process provide better process control and reproducibility. Torque measurement demonstrate to be a reliable control method in relation to mass resistance. In order to determine wet granulation end-point the Project Management Institute (PMI®) methodology was used. PMI® comprise of five main steps in the process; initiating, planning, executing, monitoring and controlling, and closure. This research pursue to improve and determine the wet granulation end-point of a drug product. PMI® methodology brings a structure and the tool to identify and solve the problem.*

Key Terms *— Automation, End-Point, Torque, Wet Granulation.*

PROBLEM STATEMENT

Mylan is a global pharmaceutical company committed to setting new standards in healthcare and providing 7 billion people access to high-quality medicine. Its robust portfolio consists of more than 7,500 products, including prescription generic, branded generic, brand-name biosimilar drugs, as well as over the counter (OTC) remedies. The company core purpose model is providing universal access to medicine. 40% of the HIV+ patients and 60% of the world's HIV+ children depends on one of Mylan's products. The company directly impacts the health and safety of patients. They protect patients and consumer health by ensuring the quality and safety of its products.

Mylan's Caguas site is a full Good Manufacturing Practice (GMP), regulated by the U.S. Food and Drug Administration (FDA). It is an oral solid dosage form plant divided in two major operations, Manufacturing and Packaging, which produces tablets, capsules, and liquid capsules of non-high potency (NHP) and high potency (HP) products. Caguas manufacturing operation area is comprised of multiple production technologies such as weighing, blending, dry granulation, wet granulation, milling, drying, slugging, compacting, compression, coating, encapsulation, liquid encapsulation, and imprinting. Each of these technologies are performed by qualified manufacturing operators in three 8-hour shifts.

Wet granulation is one of the most challenging technologies, since it directly manipulates or improves the flowability and compressibility of the powders to prevent segregation of the blend components [1]. The granules' particle size is affected by the quantity of granulation solution and flow rate and mixing time [2].

70% of Mylan Caguas's HP products are manufactured by wet granulation method using Low Shear and High Shear granulators. Its Low Shear granulation is performed using a Hobart Mixer equipped with a four-speed agitator that moves in translation and rotation modes. The agitator's speeds range from 46 to 265 RPMs. The Hobart mixer can be operated at a variable speed.

The manufacturing process of our Diamond tablets product "XA" involves the following process stages: Weighing ⇒ Low Shear Granulation ⇒ Drying/Milling ⇒ Final Blending ⇒ Compression ⇒ Film Coating. The granulating process involves

the addition of a granulating solution to a mixing powder over a specified time at a fixed mixing speed. Moisture from the granulating solution is incorporated into the granulation by adding binder solution and additional water. The quantity of water added and the mixing time influence the granulation's moisture content and liquid saturation.

The formulation contains more than 80% of low bulk density API, which directly depends on additional amount of water and mixing time to be transformed into granules. This material physical property (tapped bulk density), in combination with poor flowability and compressibility, contributes to produce tablets with physical defects such as sticking, producing several down-times, re-work, investigations, and product loss, including rejection of whole lots. Some batches did not meet acceptance criteria for in-process final blend critical quality attributes of tapped bulk density test. Statistically, 70% of the batches produced of product "XA" has at least one down-time due to tablets with sticking during the compression process. In addition, a quality investigation is generated for approximately 50% of the batches due to physical defects (sticking), tapped bulk density Out of Specification (OOS), exceeding Acceptance Quality Limit (AQL) and/or percent yield Out of Tolerance limits (OOT). These rejections already cost the company around $3 million just in raw materials and API.

The current technique used for wet granulation end-point determination for Low Shear Granulator is "manually" extracting a sample, compressing it between their fingers and evaluating it "by eye." This is the "traditional" technique (hand-squeeze test), which is subjected to individuals mainly on operator experience, resulting in poor reproducibility and process variability.

RESEARCH DESCRIPTION

This design project proposal will focus on design and implementation of a granulation end-point for product "XA." This will include, but not be limited to selecting the most effective end-point determination technology for the site's Low Shear granulator equipment, experimental and/or monitoring trials, data collection, data evaluation by statistical approach, evaluation of critical quality attributes, critical quality parameters, end-point determination, and recommendations implementation. It is intended to upgrade wet granulation end-point from hand-squeeze test to a mixer granulator measure value with automatized equipment. The project's main goal is to standardize the process execution to provide accurate granulation instructions to the manufacturing operators in which the process completion is not human-dependent. Also, to improve production efficiency, productivity, to mitigate physical defects, and cycle time. The main idea is that the equipment stops when the determined end-point value is reached.

RESEARCH OBJECTIVES

- Identify the most effective end-point granulation technology for the site's low shear granulator equipment.
- Avoid or mitigate future quality investigations, tablet defects, lot rejection and human error.
- Determine the root cause of tapped bulk density failure and the tablets sticking.
- Improve cycle time per step to assure continuous product supply.
- Design an automatized process; provide process control and reproducibility.
- Implement appropriate granulation end-point.

RESEARCH CONTRIBUTIONS

This project directly supports Mylan's mission to provide people access to high-quality medicine. Also, it contributes with the "Right First Time" initiative to assure continuous product supply reducing re-work, process variability, quality investigations, waste, cost, and cycle time. This contributes with operational excellence, a zero-defects culture and FDA regulation compliance. This should be a model to other plant sites within the Mylan organization, as well as other companies with the same problem. For example, this can enable a

research and development (R&D) team to have robust development resulting on faster drug submissions/registrations. The outcomes of this research will improve the process variability by reducing human-dependent processes. This automatized control creates a structured and standardized process that supports Mylan's pillars, which are customer service, competitive cost, quality compliance and a high-performance culture.

LITERATURE REVIEW

The pharmaceutical industry is highly regulated by the Food and Drug Administration (FDA) and other regulatory authorities. Those regulations focus on ensuring a safe, effective, high-quality, and consistent product. The most common Pharmaceutical Dosage forms include tablets, capsules, injections, oral liquids and topical.

During the manufacturing process of a drug product, production and process controls (performed by operations personnel and/or by quality control) must be stablished to ensure that the drug product has the correct strength, identity, quality and purity. The controls should include, but are not limited to sample testing, process/equipment qualifications and product specifications (in-process/finished product release testing).

Physical (physical appearance, tapped bulk density, particle size distribution, loss of drying, weight variation, thickness, hardness, friability and disintegration) and analytical testing (blend uniformity, uniformity of dosages units, assay and dissolution) can be established as a product specification.

Tablets are solid dosage forms manufactured with a combination of raw materials (excipients) with a specific pharmaceutical function such as diluents/fillers, binders, disintegrants, glidants and lubricants, and active pharmaceutical ingredients (API). Compressed tablets can be manufactured by the following three methods: dry granulation, direct compression and wet granulation [3].

Granulation is the process of a size enlargement, where individual powder particles (several different components) are combined to form larger structured particles. Granulation of one or more drugs and excipients is a common first step in the manufacturing process of tablets and capsules for pharmaceutical dug delivery. Although direct compression is possible, granulation usually ensures good flow properties and uniform bulk density essential for tableting and reducing the risk of segregation. Dry granulation, known as roller compaction, uses compressive forces to form the aggregates.

The amount of water as a liquid binder is critical for the wet granulation process, since it might result in over-wetting and weak granules. Inconsistencies in particle size of a low-density API make batch to batch reproducibility difficult either same mixing times and/or quantity of water employed.

Wet Granulation

Wet granulation is a particle size enlargement process that is frequently used in the drug product dosage forms. It comprises the massing of a mix of dry main powder particles using a granulating fluid containing a volatile solvent (which can be removed by drying) such as water, ethanol or isopropanol, either alone or in combination. The main purpose of wet granulation is to improve the flowability and compressibility of the powder mixture, ensure uniform distribution of the drug (reducing segregation), densify the powder mixture to reduce the dust and narrow the particle size distribution [1] [4].

Granulation has three main phases: nucleation and wetting (spray drops form the initial granules or nuclei), consolidation and growth (size enlargement and consolidation process), and attrition and breakage (size reduction process (attrition or fracture) (Figure 1) [5] [6].

Wet granulation Critical Quality Attributes (CQAs) include particle size distribution, powder density and loss on drying (LOD); and Critical Processing Parameters (CPPs) include, but are not limited to granulation mixing time/speed, granulation solution infusion rate and quantity of additional water.

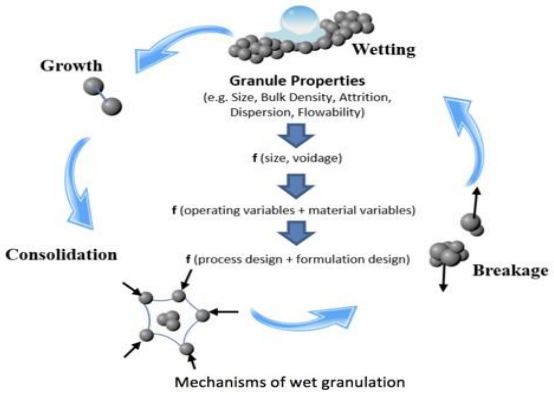

Figure 1
Mechanism of Wet Granulation

The granulation process can be employed by the three main methods: low-shear granulator, medium-shear granulator and high-shear granulator. For the purpose of this design project, we will focus on low-shear granulators.

Low-Shear Granulator Equipment

Low-shear granulators produce less shear than medium- or high-shear granulators, due to the agitator's speed, sweep volume or bed pressures. Some examples of low-shear granulators are ribbon-and-paddle blenders, planetary mixer granulators, orbiting screw granulators, sigma blade mixers and rotating shape mixer/granulators [1].

The wet granulation process of product "XA" is performed using a Hobart mixer (planetary mixer granulator) that consists of a mixing bowl equipped with a 4-speed agitator that moves in translation and rotation mode (Figure 2). The agitator's speeds range from 46 RPM to 265 RPM. The Hobart mixer can be operated at a variable speed. Generally, the slower speed is used to mix powders, and faster speeds are used for the kneading action required during the wet granulation process.

The wet mass is screened to form discrete granules, which typically are dried in a tray dryer (oven). The dried granules are rescreened or milled to the required size, blended with extra granular excipients, lubricated and compressed.

Low-shear granulation is preferred over high-shear granulation when porous granules and faster disintegration/dissolution times are required.

Figure 2
Hobart Planetary Mixer

Factors Affecting Granulation Process

The granulation process can be affected by processing variables and formulation variables. Processing variables, such impeller's speed, granulation solution infusion flow rate, quantity of purified water infused and wet massing time, directly affect the final tablet's performance.

To increase the granule's particle size, the quantity of purified water and the high impeller's speed must be increased, and wet massing time must be reduced. Impeller speed and wet massing time influence granulation compressibility [1].

The granulating solution's infusion rate and method—optimal quantity of binder solution and mode of addition (atomization/droplet), granulator size and design (mixing bowl shapes and impeller blades), load of granulator bowl (fill ratios, impeller speed, chopper speed that directly can influence granule property), impeller/chopper design (chopper cut lumps into smaller pieces and help to distribute the binder), wet massing time—must be taken into consideration during the development [7] [8].

Binder classifications (natural, semisynthetic, and polysaccharides and sugars), binder efficiency (property of drug binders—granule strength, porosity and consolidation rate), and binder concentration and liquid infusion rates (granules size can be determined based on solution flow rate) are examples of formulation variables.

End-point

End-point can be defined as a desired physical property such particle size or distribution. A wet

granulation end-point should be defined empirically in terms of wet mass density and viscosity, particle size distribution, flowability or tableting parameters. Wet granulation end-point determination advantages include process optimization, and batch-to-batch reproducibility (consistency).

End-point is difficult to determine scientifically. The most common method used by skilled operators is the "hand-squeeze test," in which a small amount of material is squeezed in one's hand and subjectively observed (Figure 3). The pharmaceutical industry employs several approaches for wet granulation end-point determination, such as indirect and direct measures [9].

Figure 3
Hand-Squeeze Test

Low-Shear Granulator

Indirect measures monitored electrical and mechanical parameters of the motor and direct measures monitored physicochemical properties of the powders.

The electrical characteristics of the motor are current and power consumption. The mechanical characteristics of the motor are torque and tachometry. The following properties can be measured in a mixer granulator: current (ineffective load indicator, it can be used for small-scale direct, or DC, motors, and do not have significant change), voltage (no relation to load), capacitance (response to moisture distribution and granule formation), conductivity (which quantifies uniformity of liquid distribution), shaft speed (no significant effect on the mean granule size), impeller/motor shaft speed (work being done on the material indicator), power consumption (measured by a watt transducer or a power cell) and impeller torque (preferable for planetary mixer instrumentation, since it's an excellent in-line measure of the load on the main impeller).

The motor's power consumption is easier to measure, is inexpensive, and installation has nearly no down-time. Impeller torque is closer to where the action is, and is directly related to the load on the shaft (not affected by mixer conditions).

The torque or power consumption pattern of a mixer is a function of the viscosity of both the granule and the binder. As viscosity increases, the need to stop the mixer at the exact end-point since the signal reaches steady state also increases.

Automation of Manufacturing Processes and Operations

Automation "self-acting" can be defined as the process enabling machines to follow a predetermined sequence of operations with little or no human intervention and using specialized equipment and devices that perform and control processes and operations [10].

Automation goals include, but are not limited to improving reliability, accuracy and productivity; improving quality; reducing human involvement; and raising the level of safety for personnel.

Programmable Logic Controllers (PLCs) eliminate the need for relay control. They perform reliably in industrial environments

PROJECT METHODOLOGY

A methodology is a system of practices, techniques, procedures and rules used by those who work in a discipline. This design project will be performed using Project Management Institute (PMI®) methodology. PMI® has nine popular methodologies: agile, scrum, Kanban, scrumban, lean, extreme programming (XP), waterfall, prince2, and PMI's PMBOK. PMI® comprises of initiating, planning, executing, monitoring and controlling, and closure [11].

During the initiating phase, a project charter was performed. A project charter is a statement of

the scope, objectives and participants in a project. It provides a preliminary delineation of roles and responsibilities, outlines the project objectives, identifies the main stakeholders and defines the authority of the project manager. It serves as a reference of authority for the future of the project.

In the planning phase, scope and budget must be defined; a work breakdown structure, Gantt chart, communication plan and risk management assessment will be prepared and established as required.

During executing phase, the historical data of product "XA" will be collected and evaluated in order to choose the granulation end-point measurer. Upon identifying the end-point granulation measuring equipment, this equipment will be purchased, installed and qualified (PQ, OQ and IQ). Experiments or process monitoring will be conducted, and data will be collected and analyzed to select subject granulation end-point for product "XA."

During the monitoring and control phase, monitoring of the manufacturing process using the subjected granulation end-point equipment and value will be conducted. Final recommendations will be applied based on the outcomes of experiments and/or monitoring activities, including, but not limited to process reproducibility tapped bulk density test compliance and/or tablets without physical defects. The project will be properly tracked, and status will be provided as previously stated in the communication plan. The recommendations will be included and implemented in a Master Formula Sheet and/or Standard Operating Procedures (SOPs), as applicable. Granulation end-point will be included in the Continuous Process Validation (CPV) Program to monitor critical quality attributes/key performance indicators and see if the process is in control as per statistical evaluation after the improvement.

During the project's closure, a report will be generated, valuable team members will be recognized, and there will be a meeting to evaluate the project and recognize any failures (lessons learned).

RESULTS AND DISCUSSION

The results obtained through the five phases of the PMI® methodology.

Initiating

As part of this Initiating phase the project charter tool was performed. The results were illustrated in Table 1.

Table 1
Project Charter

Problem Statement	Product "XA" exceeds the AQL acceptance criteria for the tablets' visual critical defects, resulting in process re-work and low yield.
Goal	To design and implement appropriate granulation end-point.
Business Case	The improvement will minimize physical visual critical defects, cycle time and yield.
Scope	Improve manufacturing process of product "XA"

Planning

Scope and budget, work breakdown structure, Gantt chart, communication plan, and risk management assessment were defined and approved.

Executing

A total of 12 lots of product "XA" API were evaluated for particle size (d50 and d90) and tapped bulk density. Based on API statistical evaluation for product "XA" sticking level, the following conclusions were reached:

- If d50 increases, sticking level tends to decrease. / If d50 is below 20%, it will cause sticking.
- If d90 increases, sticking level tends to decrease. / If d90 is below 80%, it will cause sticking.

Particle size ranged from 28 µm to 58 µm for d50, and 91 µm to 166 µm for d90, and bulk density ranged from 0.39 g/mL to 0.55 g/mL.

As per the instructions in the Master Formula Sheet (MFS), the operator must granulate until acceptable granulation is achieved. The current technique used for wet granulation end-point determination for Low Shear Granulator is "manually" extracting a sample, compressing it between their fingers and evaluating it "by eye." This is the "traditional" technique (hand-squeeze test), which is subjected to individuals mainly on operator experience. Research was done in order to select the most effective end-point determination technology for the site's low shear granulator equipment.

After the evaluation was performed, a torque measurer was selected to establish the end-point for product "XA." With the torque measurer, we can monitor the torque drawn by the impeller. As the granulation nears its end-point, torque rises steeply. The torque curve formed is correlated with a defined end-point.

Design, Installation and Equipment Qualification

The torque measurer (HMI, VFD and PLC) was installed in a Hobart Mixer Model V1401. The Design Qualification (DQ) was applied to the equipment. The results obtained from the DQ document for the Hobart Mixer after the installation of torque measurer (HMI) complied with the requirements and the current design.

The execution of the Installation, Operational, and Performance for the Hobart Mixer Model: V1401 after the installation of the Torque Control System was successfully completed.

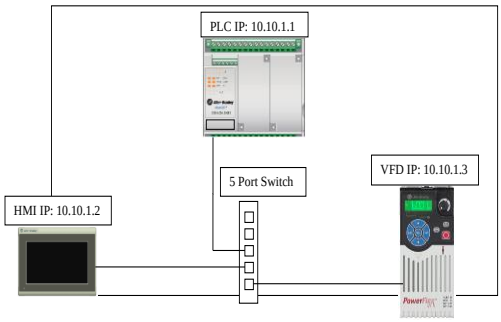

Figure 4
Torque Measurer System

The Hobart Mixer system consists in one HMI PanelView 800, one PLC Micro 820 Controller and one VFD PowerFlex 525, connected to an Ethernet/IP Network that should linked with the machine PLC embedded Ethernet Port (Figure 4).

The Hobart Mixer with a Torque Control System HMI provides to the manufacturing operator three Blending Cycle Mode options as follows:

- **Time Mode:** The equipment stops automatically once the time setpoint value is reached.
- **Torque Mode:** The equipment stops automatically when the torque setpoint value is reached.
- **Time & Torque Mode:** The equipment stops automatically when either time or torque is reached first.

Monitoring

Granulation of monitoring batches was performed following the instructions established in the Master Formula Sheet, and the torque measure was concurrently monitored in order to determine the torque value that represents the granulation end-point of product "XA."

Statistical focused on the torque values obtained from additional Purified Water, Additional Mixing Time at speed #2 based on operator documented data (1 minute each) and final blend tapped bulk density (200X).

Monitoring batches of product "XA" were manufactured using the same raw materials releases numbers and a combination of at least two different API release numbers per batch (as required).

As shown in Figures 5 to 7, process variability on torque outcomes—APW (7 Nm and 342 Nm) and G2 (7 Nm and 665 Nm). Except for one batch, all monitoring batches met the final blend physical testing acceptance criteria (physical appearance, tapped bulk density, and moisture). Tapped bulk density (200X) ranged from 0.67 g/mL to 0.79 g/mL. A value of 0.59 g/mL was obtained for one batch. For this batch, torque outcome shows very low values (median APW 10 Nm and G2 12 Nm) in

comparison with batches 1 and 2 (median APW 135 Nm and G2 448 Nm).

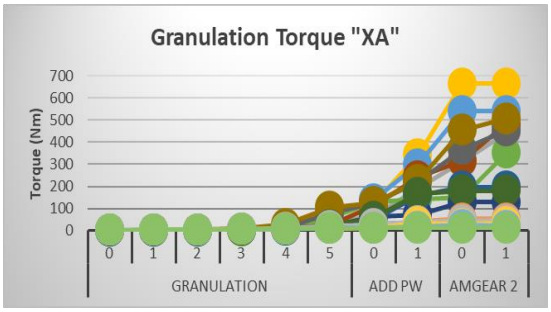

Figure 5
Batches 1 and 2 Torque Measures

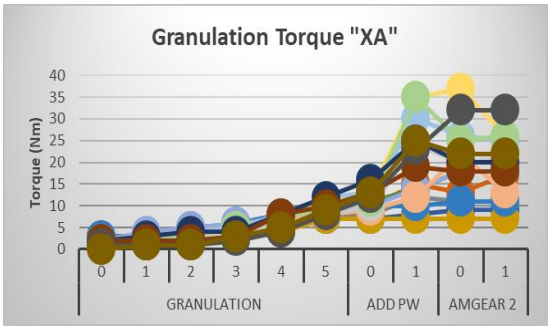

Figure 6
Batches 3 and 4 Torque Measures

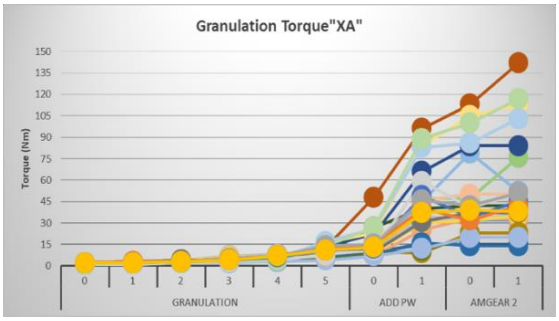

Figure 7
Batches 5 and 7 Torque Measures

It was noticed that three batches had tapped bulk density results too near to the lower limit. Also, batches that obtained tapped bulk density lower than and equal to 0.70 g/mL showed physical defects during the compression process. Nevertheless, no physical defects were observed for batches that obtained tapped bulk density higher than and equal to 0.70 g/mL.

Lower torque measure data shows that the granulation of batches requires either additional water, additional mixing time and/or a combination of both. Therefore, based on the torque measures data obtained, we can conclude that higher torque values produce higher tapped bulk density results, resulting in less or none tablets with physical defects.

Due to torque measure variability, the median will used to determine the best torque measure if central tendency. The median is the middle score for a set of data that is less affected by outliers and skewed data. Therefore, based on the statistical evaluation, the following were recommended:

- **Additional Purified Water (APW)**: 135 Nm will be subjected as APW end-point torque.
- **Additional Mix at Gear 2 (G2)**: 448 Nm will be recommended as G2 end-point torque.

Monitoring and Control

Monitoring activities using the subjected torque granulation end-point were performed in order to confirm the process reproducibility and/or to evaluate is an adjustment on the torque values is required for centralization purposes. A Technical Assessment Report will be generated with the data compilation, evaluation, and final recommendations.

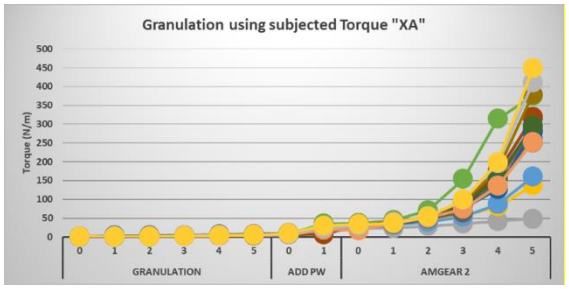

Figure 8
Batches 1 and 2 Torque Measures using Subjected Torque Set Point

Monitoring batches met the final blend physical testing acceptance criteria (physical appearance, tapped bulk density and moisture), even if not all the parts reached the subjected torque (due to API low density). Tapped bulk density (200X) ranged from 0.77 g/mL to 0.79 g/mL. During the compression process, no physical defects were observed in the tablets. In addition, monitoring batches complied with the acceptance criteria for analytical Finished Product specifications.

Therefore, it can be concluded that the subjected torque granulation end-point of 135 Nm (additional

purified water) and 448 Nm (additional mix at gear 2) are adequate. Batch-to-batch consistency and reproducibility was achieved regardless of raw materials and API physical conditions (low density). Nevertheless, since only one of the 16 parts reached the G2 subjected torque value, an adjustment to the granulation end-point will be performed for centralization purpose.

For centralization purposes, the average will be used to determine the best torque measure (if central tendency). The average is defined as the number that measures the central tendency of a given set of numbers. Based on the statistical evaluation, the following were recommended:

- **Additional Purified Water (APW)**: 91 Nm will be recommended as APW end point torque.
- **Additional Mix at Gear 2 (G2)**: 347 Nm will be recommended as G2 end point torque.

CONCLUSION

This project validated the use of the PMI® methodology for the granulation end-point determination of a drug product of oral dosage. The PMI® methodology brings a structure for the improvement process.

Based on the satisfactory physical characteristics (tapped bulk density and physical defects) and torque measurer data evaluation of product "XA" batches, we conclude the following:

- Torque measurer subjected end-point values successfully demonstrates granulation completion. This means that the quantity of additional water, additional mixing time and/or a combination of both were adequate.
- Torque measurer subjected end-point for both steps, additional purifier water and additional mixing time, resulted on tapped bulk density (200X) higher than 0.70 g/mL with less than or no tablet defects.
- Subjected torque value assured batch-to-batch consistency, control and reproducibility in either raw materials' physical characteristics and/or human intervention.
- This automatized control creates a structured and standardized process.

We can conclude that the subjected torque granulation end-point of 91 Nm (additional purified water) and 347 Nm (additional mixing at gear 2) for product "XA" are adequate and show batch-to-batch consistency and reproducibility regardless of raw materials and API physical conditions (low density).

The goal to determine the granulation end-point using the PMI® methodology was achieved successfully, based on the results.

RECOMMENDATIONS

To improve the manufacturing process and minimize the final blend tapped bulk density out of specification (OOS) and compression tablets' physical defects, it is recommended to update the Master Formula Sheets of product "XA" to include the subjected torque setting (based on statistical evaluation and monitoring satisfactory results).

In addition, it is recommended to extend the wet granulation end-point determination to other Mylan LLC Caguas products as required.

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