Wet Granulation End-Point Determination of a Drug Formulation

Author: Yaritza Merced Vega
Advisor: Carlos Gonzalez, Ph.D.
Department of Industrial Engineering

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). 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. This research pursue to improve and determine the wet granulation end-point of a drug product.

Introduction

Mylan is a global pharmaceutical company committed to setting new standards in healthcare and providing 7 billion people access to high-quality medicine.
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].
70% of Mylan Caguas's HP products are manufactured by wet granulation method using Low Shear and High Shear granulators.

Objectives

This design project proposal will focus on design and implementation of a granulation end-point for product "XA."
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.

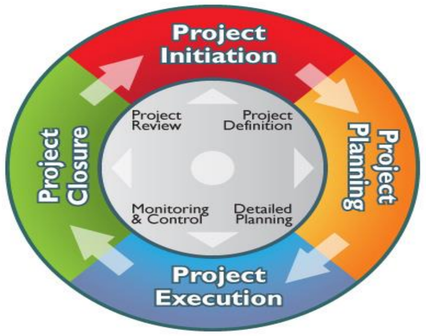
Problem

Product "XA" 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,
- ❖ product loss,
- ❖ rejection of whole lots.
- ❖ not meet acceptance criteria for in-process final blend critical quality attributes of tapped bulk density test.

Methodology

This design project will be performed using Project Management Institute (PMI®) methodology.



Results and Discussion

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

Initiating Phase

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"

Executing Phase

After the evaluation was performed, a torque measurer was selected to establish the end-point for product "XA."

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 1).

Figure 1: Torque Measurer System

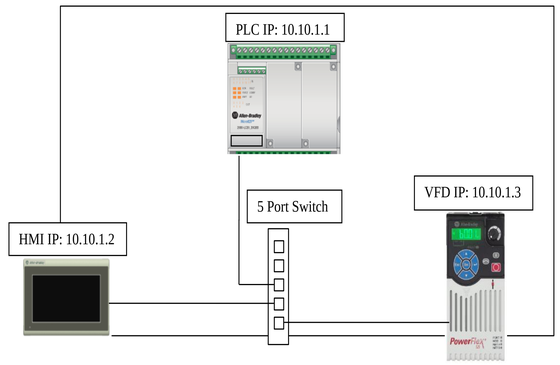


Figure 2: Batches 1 and 2 Torque Measures

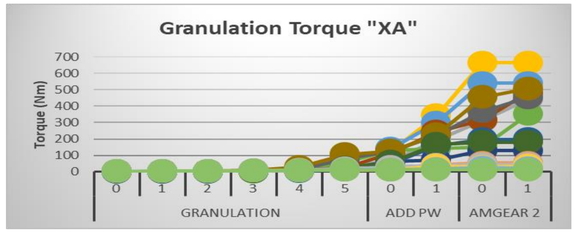


Figure 3: Batches 3 and 4 Torque Measures

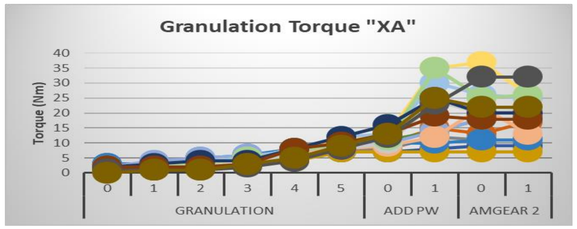
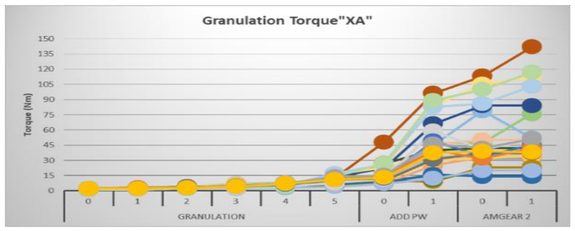


Figure 4: Batches 5 and 7 Torque Measures



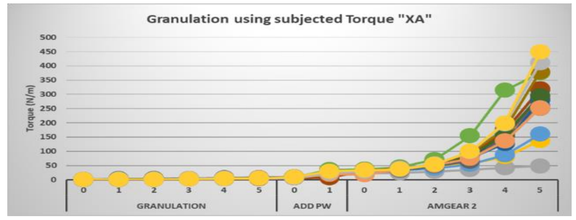
Based on the statistical evaluation, the following were recommended:

- ❖ **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 Phase

Batch-to-batch consistency and reproducibility was achieved regardless of raw materials and API physical conditions (low density).

Figure 5: Batches 1 and 2 Torque Measures using subjected Torque



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.

Conclusions

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.
- ❖ The subjected torque granulation end-point 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.

Future Work

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.

References

[1] *Handbook of Pharmaceutical Granulation Technology*, 3rd ed, D. Parikh, Ed. Maryland, USA: DPharma Group Inc., 2010.