Optimization of Pharmaceutical Product Production Lots at Granulation Manufacturing Stage

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Abstract *— The customer of ABD Company wants the CY product to meet 7% 40 mesh requirement in 80% of the lots requested. The company has two granulators that are used for the manufacturing of the product but one of them typically produces higher 40 mesh values than the other one. A project to understand the situation was proposed and tools from DMAIC methodology were used. It was found out with the investigation that the granulator that produced higher values had a different humidity setpoint which caused more water to be needed in the manufacturing process. It is understood that coarser particles are a result of water excess. A change in the humidity setpoint was recommended as a solution of the problem and to harmonize both equipment. Once the change is implemented it should be monitored to see the results after the change.*

Key Terms *— DMAIC, Granulation, Improvements, Pharmaceutical Industry*.

PROBLEM STATEMENT

Pharmaceutical companies are continuously looking for ways to improve their processes and products, and this is the case of company ABD. CY is an oral suspension antibiotic manufactured by ABD for a third-party customer that requires 80% of the product demand to meet NMT 7% 40 mesh criteria. Currently, the production of lots with NMT 7% 40 mesh material in one of the granulators has been variable, affecting the supply for the customer since the lots that do not meet the criteria need to be re-sifted and this consumes time and resources. The scope of this project will be focused on the identification of the root cause of the problem and the development of a plan to solve it, the implementations of the solutions are out of scope.

Research Description

The purpose of this project is to identify what is causing the unpredictable performance of the product and propose permanent solutions to ensure reliable production. This will result in great benefits for the company since the customer will be satisfied with the on-time supply of the product and the re-sifting process will be eliminated. The elimination of the re-sifting process will result in cost avoidance and cycle time improvements for the company.

Research Objectives

The objectives for this project are to properly identify solutions to improve by 30% the production of lots with NMT 7% 40 mesh material and develop a plan to implement those identified solutions.

Research Contributions

With this project, company ABD will have permanent solutions to improve the manufacturing process of product CY and will fulfill customer needs by on-time delivery and product meeting their requirements. The improvements will result in a cost avoidance of approximately $700K and in cycle time improvements of about 1,440 hours/year by the elimination of the re-sifting process. With these improvements, the process will be more robust and in control.

LITERATURE REVIEW

The changes in technology, economy, diseases, etc. are causing the pharmaceutical industry to look for improvements in their processes. These improvements could be for cost savings purposes, to develop new products for the market or for manufacturing flexibility, among other things. Since pharmaceutical industries are strictly regulated by many agencies, these changes need to be carefully

developed and implemented, always assuring compliance with regulations.

Pharmaceutical industries can manufacture drugs in different dosage forms. A dosage form is the mean by which drug molecules are delivered to sites of action within the body [1]. They can be classified by route of administration and physical form and Figure 1 shows examples of them.

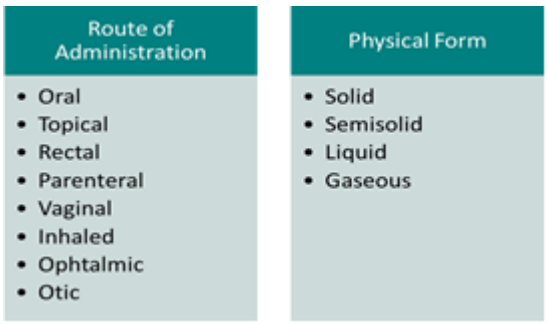

Figure 1
Classification of Dosage Forms

Drugs in solid dosage form are mainly administrated orally and in different types: tablets, capsules, powders, among others. Tablets are hard and compressed drugs that come in many shapes and colors. Capsules are a medication in a gelatin shell that can be classified in two types: hard shelled and soft shelled. A pharmaceutical powder is a mixture of finely divided drugs and chemicals that can be meant for internal or external use [2]. They are usually dispersed in water or dissolved before taking. To manufacture any of these types of dosage forms, pharmaceutical industries have regulated processes, some longer and complicated than other ones.

Granulation

Usually the first step in pharmaceutical manufacturing is the granulation process. Granulation is the process of particle enlargement by agglomeration technique that transforms fine powders into free-flowing, dust-free granules. Typically, granulation starts with a drug mixing of powder ingredients along with the active pharmaceutical ingredient (API) [3]. Granulation can be divided in two main types: wet granulation and roller compaction. Roller compaction is a completely dry process that eliminates the need for an additional unit operation of drying. On the other hand, wet granulation has a binder in its formulation that helps improve the compaction characteristics of the granulation. It is the preferred method for formulations with high drug loading since most APIs have small particle size and have problems with flow and sticking to surfaces. Wet granulation can be conducted in three main ways: low shear, high shear and fluid bed granulation [4]. Most of high shear granulators have a mixing bowl, an impeller, an auxiliary chopper, a motor, and a discharge port, see Figure 2. The bowl may have a jacket to control the temperature by circulating hot or cool liquids. Some of the advantages are [5]:

- Short processing time
- Reproducibility of uniform granule size distribution
- Dust reduction
- Predictable end-point determination

Figure 2
High Shear Granulator

Drying

After the granulation step is finished, a drying process is needed. This step is frequently performed in a fluid bed dryer (FBD). An FBD is used to reduce the moisture content of pharmaceutical powders or granules. It functions by introducing hot air at high pressure, the wet solids are lifted from the bottom and suspended in a stream of air, thus heat transfer is

accomplished by direct contact between the gases and the solids [6]. Fluid bed dryers were designed to dry materials quickly; when running at optimum conditions they can dry in minutes while tray dryers require hours [7].

Figure 3
Fluid Bed Dryer

Milling/Sizing

Milling is a key step in the manufacturing process of solid dosage forms for size reduction in wet granulation before drying and dried particles before tableting. Some of the advantages of dry sizing are:

- Particle size calibration for uniformity.
- Achieve narrow particle size distribution curve.
- Increase surface area.

The size of a particle or granule is reduced by fracturing the material using one of the following forces: shear, compression, impact or tension. These forces come from different types of mills. The horizontal hammermill introduces the material perpendicularly to the rotating shaft and material sizing is accomplished through the direct impact with steel bars. Oscillating granulators provide low shear size reduction by using oscillating bars. Material is reduced by pressuring the material between the bars and the wire mesh screen. Figure 4 shows an example of a mill used in the manufacturing industry.

Figure 4
Mill

There are two important factors that affect the particle size of a material: impellers and screens. A round bar impeller is better for dry granulations while a square arm impeller is good for both wet granulation and most dry granulations. The type of the screen is also very important, and many hole geometries have been developed for flexibility in the desired particle size distribution. Round hole geometry is the most common and is used to size reduce or delump dry material. The characteristics of the material and the final particle size distribution wanted must be taken into consideration when selecting a screen. The general approach is to select a hole diameter that is two steps larger than the desired particle size target [8].

Coating

Many industries like the pharmaceutical, chemical, agricultural, etc. have been utilizing particle coating methods during many years. Pharmaceutical industries use this method to control the drug release from different oral dosage forms designed to have either an enteric, timed, or sustained release effect. They use it also to block the unpleasant taste of drugs and to make them more eye-catching with colors. Some of the advantages of this process are: quicker operation, uniformity of the coating, and that it can be used to coat particles that vary in size, shape, and density [9].

Blending

The blending process is of critical importance to create a uniform mixture of the API and excipients

and assure it does not segregate in order to deliver the right dose of the medicine to the patient. It involves the random movement of particles during an established amount of time. Blending can occur by three mechanisms:

- Diffusion: redistribution of individual particles by random movement relative to one another.
- Convection: movement of particles from one place to other within the blend.
- Shear: change in the configuration of ingredients through the formation of shearing strains within a bed of material.

A blender has the purpose of homogenizing the material until a certain point of uniformity to consequently produce a material of acceptable quality. There are many types of them: tumble, high shear, screw/paddle, pneumatic, and continuous blenders. Tumble blenders operate by reorienting particles in relation to one another when they are placed in motion and they can function by diffusion or convection mechanism. Examples of tumble blenders are V-blenders (Figure 5) and Bin blenders [10].

Figure 5
V-Blender

Six Sigma

Six Sigma is defined as "a rigorous, focused and highly effective implementation of proven quality principles and techniques" (Pyzdek, 2003). The term sigma (σ), a Greek letter, is used by statisticians to measure how the process variates. Basically, Six Sigma aims for almost free error performance, or more specifically, 3.4 problems per million opportunities. Its principle is that by reducing variation, defects can be reduced and therefore improvements in productivity and profits can be achieved (Austin, 2013). Six Sigma is applied with a performance improvement model known as DMAIC, which is described as follows [11]:

D	Define the goals of the improvement activity.
M	Measure the existing system.
A	Analyze the system to identify ways to eliminate the gap between the current performance of the system or process and the desired goal.
I	Improve the system.
C	Control the new system.

Figure 6
DMAIC Process

METHODOLOGY

The following methodology seeks to meet the two objectives previously mentioned:

- Identify solutions to improve by 30% the production of lots with NMT 7% 40 mesh material.
- Develop a plan to implement the identified solutions.

To comply with these objectives, some tools of the DMAIC methodology will be used. As previously mentioned, DMAIC has five phases with different tools that help identify the root cause of problems and determine solutions for it. For this project, tools from the first three phases will be utilized. Tools from the Define phase like project charter, SIPOC, voice of the customer and communication plan will be used. These tools will help in the understanding of what the customers need and their requirements, what are the expected benefits from the project and the timeframe for completing it. From the Measure phase, a data collection plan will be used to gather and organize data of the equipment used and the process to understand its performance. Data will be acquired from different sources and systems used in the company. Once all data has been collected, it will be analyzed using charts and graphs to provide visual indications of problems. These charts will help in the

identification of the root cause of the problem. After the problem has been identified, then recommendations will be provided and a plan to implement them will be designed.

RESULTS AND DISCUSSION

One of the tools used from the Define phase was the Project Charter and it is shown in Table 1. It was used to describe the project with detailed problem and goal statements, business impact or benefits of it, and who the members were. This project charter was discussed with the stakeholders, so they could be aware of the project and its benefits and it was approved by them.

Table 1
Project Charter

Project Title: Optimization of Pharmaceutical Product Production Lots at Granulation Manufacturing Stage		
Project Sponsor	**Project Lead**	
Iddys Figueroa	Michelle Marrero	
Problem Statement		
The production of lots with NMT 7% 40 mesh material in Gral 2 has been variable. This unpredictable performance affects the supply for the third-party customer who requires approximately 80% of the product demand to meet the 7% requirement due to market needs.		
Goal Statement		
Increase the production of lots with NMT 7% 40 mesh particles in Gral 2 to achieve 80% of lots meeting this requirement and identify permanent solutions to ensure reliable production. This implies a 30% improvement from current performance which is around 50% of lots.		
Business Impact		
- Customer satisfaction by fulfilling customer needs. - Cost avoidance by elimination of re-sifting process causing yield material losses of ~27% per lot ($20K) - Cycle time improvements by elimination of the re-sifting process time of approximately 3 shifts per resifted lot, meaning 1,440 hours per year.		
Core Team Members	**Project Role**	**% of Time**
Michelle Marrero	Lead	50%
Edward Avilés	Co-Lead	20%
Isamar Moreno	Team Member	10%
Jose Juan Pacheco	Team Member	10%
Juan Vélez	Team Member	10%
Iddys Figueroa	Sponsor	10%
Additional Stakeholders		

Position	**Functional Area**	**Impact**
Director	Supply Chain	Impacted
Director	Operations	Owner
Director	Engineering	Impacted
Director	Quality	Impacted

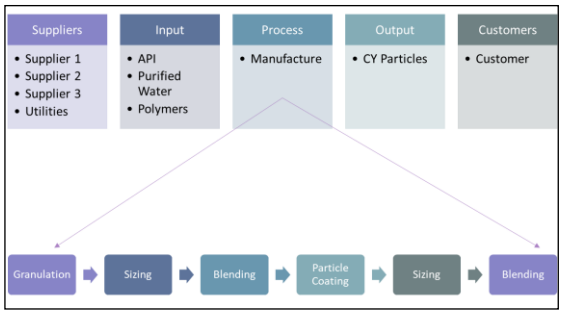

Figure 7
SIPOC Diagram

A SIPOC diagram, Figure 7, was developed to understand the process at a high level. It helped in the understanding of who were the suppliers, what are the inputs and outputs of the process and who is the final customer of the process. In every project, the voice of the customer is very important because they are the most interested in the change or improvement. In this case, the customer is very clear; they want the product to meet the NMT 7% 40 mesh requirement. The request from them is that they want to receive 80% of the lots meeting the 7%, while assuring the product is in control and complies with all the correspondent regulations.

Figure 8
Basic Process Map

To better understand the manufacturing process of CY particles, a basic process map was developed and is shown in Figure 8. It shows every step of the manufacturing of the CY particles and which type of equipment is used in each stage. The company has two granulators and every lot follows this same process, no matter in which granulator the process began. A data collection plan was established to gather important information about the process and create a baseline to monitor improvements. Data of the 40 mesh will be plotted by year in a control chart to analyze its behavior through time, also parameters of the two granulators will be compared to state their differences and understand what is causing higher 40 mesh values in the granulator 2.

Table 2
Data Collection Plan

Measure	Stratification Factor	Operational Definition	Source	Format of Reporting
Mesh 40	By year	Percent of particles retained at mesh 40	Data System	Control Chart
Parameters	By Gral	Parameters or characteristics of the granulator	Equipment	Table

Data collected from 40 mesh test of lots manufactured in Gral 2 is plotted in Figure 9. In 2016 the average was around 8% with an outstanding increase at the end of the year and beginning of 2017. This increase was because during that time the mesh used was not the correct one, but it was replaced, and the results improved significantly. Even though there was a decrease, the 40 mesh did not reach the target, which is 7.

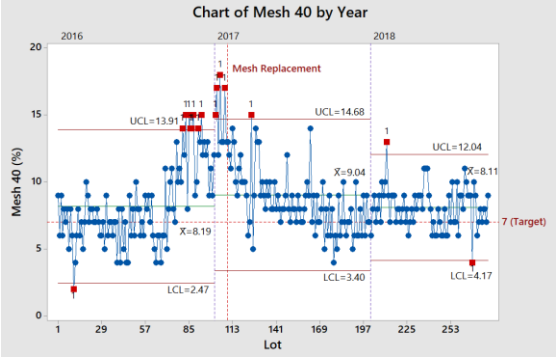

Figure 9
Baseline Data

As information was gathered to understand the differences between the two granulators, it was found out that the Gral 2 had a lower supply air humidity setpoint than Gral 1. The humidity setpoint of Gral 1 is 15 gr/lb and the setpoint of Gral 2 is 0 gr/lb. This means that the second granulator is drying the material to a lower humidity setpoint and this causes additional water to be needed in the process to reach end power in the equipment. It is understood that an excess of water can cause coarser particles. If coarser particles are produced, then they will be retained at the 40 mesh and the lot will not meet the 7% requirement. Table 3 summarizes all the information gathered for both granulators.

Table 3
Comparison of Granulators

Granulation Process		
Parameter	**Gral 1**	**Gral 2**
Size	600 L	1200 L
Granulation runs	6	3
Target Batch Size	430 kg	520 kg
Supply Air Humidity Setpoint	15 gr/lb	0 gr/lb
Amount of water added in 2nd granulation	Depends on the amount of material received from the 1st granulation	90 kg of water added if 1st granulation is between 152-168 kg. If not, amount is modified.
Supply Air Temperature	90°C	90°C
Milling	3500 rpm	3500 rpm

As a recommendation, this setpoint in Gral 2 must be changed and harmonized with Gral 1. With this change the Gral 2 will not require an excess of water and will be capable of producing finer particles. The first step of this change should be an assessment to understand all the steps needed for the change, how it will impact documentation, production, etc and then create the change plan in the system. Once the change plan, and all the tasks are created and approved, then the changes in the recipe and documentation should be done. When the

change is implemented, then the result of each lot must be continuously monitored and plotted against the baseline data previously gathered to see if the trend improved and the 7% target is met as required by the customer.

CONCLUSION

Company ABD manufactures CY for a third-party customer and they received a request from them about wanting to receive 80% of the lots meeting NMT 7% 40 mesh criteria. Since approximately 200 lots of this product are manufactured per year, the company has two granulators in order to comply with the demand. For some reason, the Gral 2 typically produces lots with higher 40 mesh values than Gral 1. This results in lots needed to be resifted in order to comply with the criteria. This adds more time, money, and resources needed to finish the process. Tools from the DMAIC methodology were used in the project to understand the problem. As part of the investigation, it was found out that the Gral 2 had a lower humidity setpoint which causes more water to be needed and excess of water creates coarser particles. This project provided the recommendation of changing the setpoint, following the proper procedures, to solve the problem of the Gral 2 producing coarser particles.

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