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.

Introduction

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.

Problem

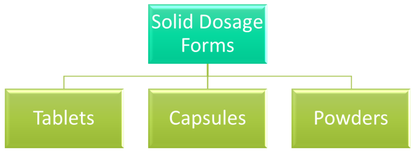
The purpose of this project is to identify what is causing the unpredictable performance of the product and propose permanent solutions to ensure reliable production. This will result in great benefits for the company since the customer will be satisfied with the on-time supply of the product and the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

Background

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:

Route of Administration	Physical Form
• Oral • Topical • Rectal • Parenteral • Vaginal • Inhaled • Ophtalmic • Otic	• Solid • Semisolid • Liquid • Gaseous

Background (cont.)

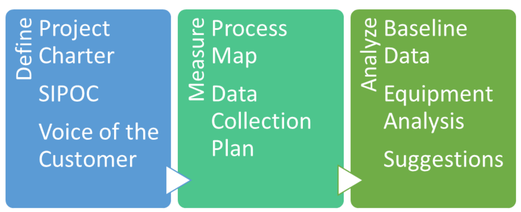


A pharmaceutical powder is a mixture of finely divided drugs and chemicals that can be meant for internal or external use [2]. To manufacture any of these types of dosage forms, pharmaceutical industries have regulated processes, some longer and complicated than other ones. Usually the first step in 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.
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. Six Sigma is applied with a performance improvement model known as DMAIC, which is described as follows [4]:

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.

Methodology

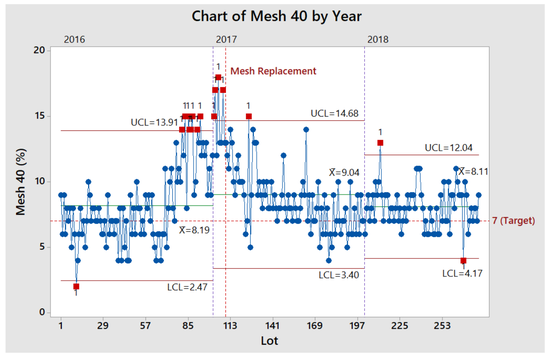
To comply with the objectives previously stated, some tools of the DMAIC methodology were used. As previously mentioned, DMAIC has five phases with different tools that help identify the root cause of problems and determine solutions for it. For this project, tools from the first three phases were utilized.



Results and Discussion

One of the tools used from the Define phase was the Project Charter. 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.
Data collected from 40 mesh test of lots manufactured in Gral 2 was plotted. 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.

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



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.

Granulation Process		
Parameter	**Gral 1**	**Gral 2**
Size	600 L	1200 L
Target Batch Size	430 kg	520 kg
Supply Air Humidity Setpoint	15 gr/lb	0 gr/lb

Results and Discussion (cont.)

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.

Conclusions

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.

Future Work

All recommendations are being implemented and the project should by finished by December 2018.

Acknowledgements

I want to dedicate this work to my family but especially to my mom, to whom I owe everything. Love you and miss you.
Special thanks to my co-workers who helped me through this journey.

References

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