Coating Process Improvement

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Abstract *— An increase in the number of events associated to AQL failure that resulted on partial batch rejections was observed in 2020 for Tablets/Caplets formulations due to cosmetic conditions such as bump on coating, color blotches, pits on tablets, rough coating, lack of gloss, and odd shape tablets/caplets appearance. This report summarizes the coating improvements and recommendations identified to reduce the amount of pans inspected/rejected caused by aesthetical conditions. To improve the quality of process outputs identified the team selected a quality management method DMAIC (Define, Measure, Analyze, Improve, and Control). After using the methodology, the purpose of improving the cosmetic appearance of the product and decreasing the impacted pans was achieved. Data presented a significant reduction of pans inspection and rejection. Tablets pans impacted was reduced from 2.8% to 1.7%. Caplets pans impacted was reduced from 1.7% to 0.2%.*

Key Terms *— Coating, Improvement, Defects.*

PROBLEM STATEMENT

An increase in the number of events associated to AQL failure that resulted on partial batch rejections was observed in 2020 for Tablets/Caplets formulations. In addition, data provided reflects an increment in inspections related to cosmetic conditions such as bump on coating, color blotches, pits on tablets, rough coating, lack of gloss, and odd shape tablets/caplets appearance. A total of 21 investigations were generated between January and August 2020 in the coating area related to the cosmetics conditions previously mentioned. As results of this situation, project was initiated to investigate the cause for the events reported and address them accordingly.

RESEARCH DESCRIPTION

Reduce manufacturing inspections and material rejection after coating process of Tablets and Caplets.

Research Objectives

The purpose of this report is to present status of Project. This report summarizes the coating improvements and recommendations identified to reduce the amount of pans inspected or rejected caused by aesthetical conditions on tablets/caplets.

Research Contributions

The project contribution consists in decreasing at least 50% of rejections and inspections caused by cosmetic conditions for all sugar-coating products. Table 1 provides the contribution of this project.

Table 1
Contributions

	Customer / Patient / Payer	Employees/Organisation
What is the positive change?	Meanwhile the patients require tablets with acceptable appearance.	- Reduce the inspection and rejection of pans. - Increase operational efficiencies and improve quality - Optimum solution in terms of uninterrupted operation of the business

LITERATURE REVIEW

Tablets and caplets are an analgesic product that contains Ibuprofen. This product is used for temporary pain relief (analgesic) and to reduce the fever (antipyretic). The active ingredient. Ibuprofen (nomenclature iso-butyl-propanoic-phenolic acid), is a non-steroidal anti-inflammatory drug [1].

Caplets are prepared by mixing drugs with a binding medium and then compressing the mixture into an oval-shaped medicinal tablet in the shape of

a capsule under high pressure. They are usually a film or gelatin-coated for masking the unpleasant odor and taste of the medicines and excipients and make them easy to swallow. The manufacturing process caplets is comprised of ten (10) unit operations: weighing, granulation, drying, milling, blending, compression, sugar coating, seal coating, polishing and branding [2]. Upon Branding process is completed the caplets are packaged in fiber drums.

Tablets are an oral solid dosage form of medicine that most commonly prescribed dosage form. They are usually circular and flat and are coated with a sugar-like material to mask the unpleasant taste and odor and to control the release rate in the body, they can come in many shapes and sizes to better accommodate the needs of patients. Manufacturing process consists of the following major stages: Weighing, Granulation, Milling, Blending, Compression, Seal Coating, Sugar Coating, Polishing and Branding/Bulk Packaging (Dumping) [3].

Tablets and caplets are very similar forms of medication. They are both coated with sugar and other ingredients to help slow down the release of medication into the body.

The Sugar-Coating process is a process for the application of thick coating layers, primarily for masking taste and enhances product appearance. This process is performed in the Drug Products Rooms 40A, 40D and 40G and during the process, syrup is sprayed onto the tablets. The introduction of process air evaporates the fluid and dries the sugar coating [3].

Coating process consists of different application stages: Warm up, Sub coat, Color and Color Closing. When the Sugar-Coating process is completed, the caplets or tablets are polished using a Polishing solution of White Beeswax and Petroleum Light. Each stage plays a role in the final purpose of the coating process, to provide a protective coat to the product, obtain aesthetic appeal, taste masking, and ease the tablet to be swallowed more easily [4].

An increase in the number of events associated to AQL failure that resulted on partial batch rejections was observed in 2020 for Tablets/Caplets formulations. As results, process Inspections and/or material rejection decision are taken based on the severe tablets/caplets appearance. This situation increases the manufacturing cost, and process cycle time for Advil Tablets and Caplets formulations.

Tablet coating defects and remedies are the crucial concern of a pharmaceutical formulation scientist. Unfortunately, several defects can arise with coatings. The following project provides helpful remedies for common issues that may be encountered.

METHODOLOGY

To improve the quality of process outputs identified, maintain cosmetic conditions at acceptable levels, and minimize variability in the manufacturing processes, the team selected a quality management method (DMAIC). DMAIC consists of five (5) phases of a process improvement project and is defined as: Define, Measure, Analyze, Improve, and Control.

The DMAIC methodology is a core component of the six-sigma methodology which will be used to maintain the aesthetic tablets/caplets conditions at acceptable levels for Tablets and Caplets.

IMPLEMENTATION

On this project and search, it was decided to divide it into the following phases:

Figure 1
DMAIC Methodology

Define Phase

In the Define phase, the project team clarified the purpose and scope of the project to improve the

aesthetic appearance of tablets and caplets after the coating process. Project Charter, Voice of the Customer, Data Collection Plan, and SIPOC six sigma tools were selected to focus on finding out directly from customer what quality is, and how well the current process meets with acceptance criteria.

During the define phase the boundary of the project was limited to the cosmetic defect categorized as color blotches, rough coating, lack of gloss, pits on tablets, and bump on coating.

Project charter was developed to define the project scope, boundaries, deliverables, and dates. This line document keeps the team focusing on the target.

Problem Statement - Investigations trend was observed during the 3 QT 2020 related to cosmetic conditions as Color Blotches and Rough Coating. On October 2020 project was issued to evaluate the situation reported on 21 investigations generated.

Project Scope

Sugar Coating and Polishing stages were evaluated to identify coating improvements that will reduce partial batches rejection and reduce the inspections performed in the analgesics area. The project goal consists in decrease at least 50% of rejections and inspections caused by cosmetic conditions for all sugar-coating products.

SIPOC (Suppliers, Inputs, Process, Outputs, and Customer) - This tool provided the team a broad view of the coating processes for sugar coating products identifying boundaries, customers, supplier relationship, input, and outputs. SIPOC was used to evaluate the process needs and identify the points most likely to collect data that will lead us to root causes and check points.

Voice of the Customer (VOC) tool identifies who the customers are, and what they need, and why they need it. The customers identified were the manufacturing area and the patients. The manufacturing area requirement is to reduce the inspection and rejection of pans. Meanwhile the patients require tablets with acceptable appearance.

Measurement Phase

During the measurement phase the team determined the information required to evaluate the magnitude of pans rejections and/or inspection for all sugar-coating products. The goal was to get enough information from the process and product to understand the most probable causes that create or influence cosmetic conditions such as bumps on coating, color botches, rough coating, pits on tablets, and lack of gloss.

Process Map displays steps to illustrate how sugar-coating processes are managed in the coating area. It is a visual representation of the workflow for the whole operation from beginning to end of sugar-coating stage. Process map provided fundamental information of the processes that helped the investigation to identify critical areas. In addition, this tool was used for the development of the baseline data collection exercise. The process map was used to identify sampling points and to initiate the FMEA tool that was used during the Analyze phase.

Data Collection plan was developed using the process map as reference. Data from the equipment logbooks (Inspection machine), AQL results, and room logbooks were evaluated.

Analyze Phase

During the Analyze step the team identified root causes that may be attributed to cosmetic tablets/caplets conditions previously mentioned. Cause and Effect Diagram (Fishbone) and FMEA tools were used to determine the most probable causes focusing on the problem statement developed. The root causes were addressed through solutions that were identified at the Improvement phase.

Cause and Effect Diagram (Fishbone) was used to systematically list all the different potential causes that can be attributed to a specific problem (or effect). This tool helps to identify the possible reason why a process fails and where to look for root causes. As part of this Fishbone analysis, the method used to determine the acceptance criteria level condition as color blotches, rough coating,

lack of gloss, pits on tablets, and bump on coating was also evaluated. The following Figure 2 display the conditions evaluated:

Figure 2
Tablet Conditions

In addition to the tablet's conditions presented on Figure 1, the amount of odd shape tablets was evaluated and quantified. Tablets capping and improperly seal coated tablets are two (2) factors that may influence in the generation of odd shape condition observed after sugar coating process. The following Figure 3 illustrates this tablet condition:

Figure 3
Odd Shape Tablet

Tablets when finish the coating process lost a considerable portion of their compression shape.

During this evaluation it was found that manufacturing area did not have control samples as point of reference (Physical standard) which could be used to compare the acceptable level of tablets/caplets conditions after coating process. As immediate corrective action, team proposed to implement a detection method using control samples that present the minimum acceptable level for conditions such as rough coating, lack of gloss, color blotches. This improvement standardizes the acceptable tablets/caplets appearance between manufacturing operators and QC laboratory analysts.

In an effort to find the most probable root causes of the tablets/caplets not meeting acceptable appearance levels, a Failure Mode and Effect Analysis (FMEA) tool was executed for the coating system located in room 40A. This FMEA establishes the relation of the coating defect as the failure mode, against the process parameters control and the device failure as potential cause. This analysis even tough was performed for room 40A is applicable to the other rooms. In addition, improvements were identified to control the equipment performance variation.

Raw Data Analysis

Analyzing the data using a frequency histogram of number of rejected and/or inspected coating pans compared with production volume provides a visual representation of the situation.

Sugar coating processes are performed on three (3) coating suites identified as rooms 40A, 40D, and 40G. The following Table 1, presents a matrix for the products validated per coating room when the analysis was conducted:

Table 1
Products per Coating Room

Product	Rooms		
	40A	40D	40G
Tablets	X	X	X
Caplets		X	X

Tablet Production Room 40A January 2020 to December 2020. %Pans impacted for inspection and/or rejection.

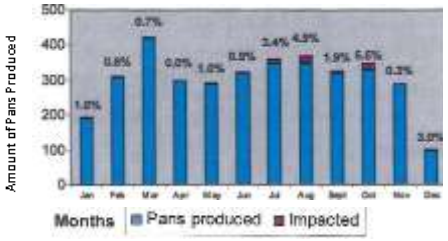


Figure 4
Frequency Histogram for room 40A (Tablets)

According to the data analyzed on Figure 4 displayed above for all pans processed in room 40A for Tablets, a total of 74 pans from 3570 pans produced (2.1%) were rejected and/or inspected during year 2020. The percent of pans inspected per

month ranged from 0.0% to 5.5%. High incidence of pans impacted was reported for the months of July, August, and October. Based on data analyzed on Figure 4, it cannot be concluded that there is a correlation between pans produced (volume) and pans inspected and/or rejected.

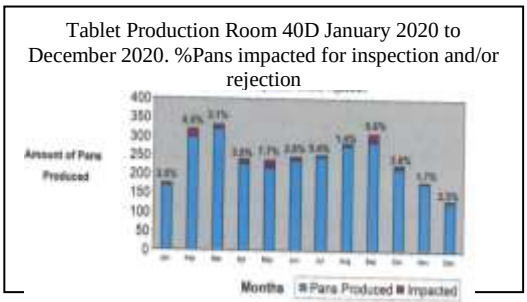


Figure 5
Frequency Histogram for room 40D (Tablets)

A total of 105 from 2830 pans (3.7%) for Tablets were rejected and/or inspected during year 2020. The percent of pan inspected per month ranged from 0.4% to 7.7%. High incidence of pans impacted was reported for the February, May, and September. Based on data analyzed on Figure 5, it cannot be concluded that there is a correlation between pans produced (volume) and pans impacted by inspection and/or rejection.

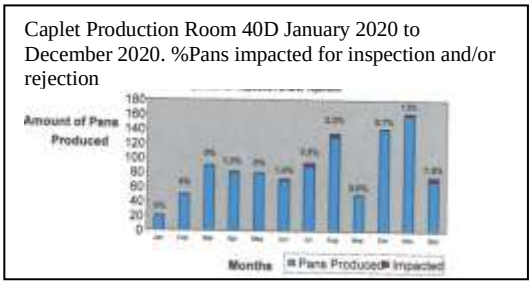


Figure 6
Frequency Histogram for room 40D (Caplets

A total of 17 from 1030 pans (1.7%) for Caplets formulation were rejected and/or inspected during year 2020. The percent of pans inspected per month ranged from 0.0% to 7.5%. An increase of pan impacted was reported for December. Based on data analyzed on Figure 6, it cannot be concluded that there is a correlation between pans produced (volume) and pans impacted by inspection and/or rejection.

Investigations

The amount of investigation generated between January — September 2020 were analyzed. According to the information collected, 21 investigations were generated for the time period mentioned. This high incidence of investigations triggers the project, which was initiated on October 2020.

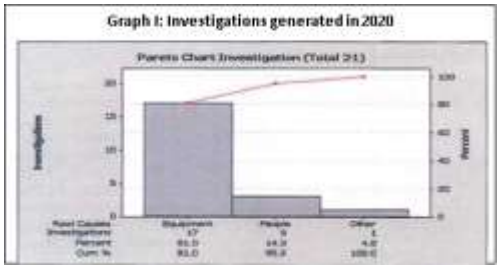


Figure 7
Investigations 2020

Based on data analyzed on Figure 7, 81% of the investigations generated associated the root cause with Equipment and 14% of investigations were attributed to People or Manpower.

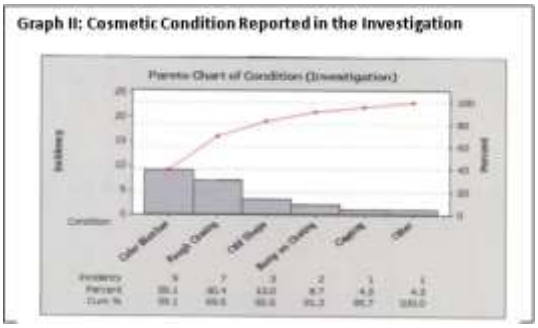


Figure 8
Cosmetic Conditions Reported

Based on data analyzed, on Figure 8 displayed above, four (4) conditions: Color Blotches, Odd Shape, Bump on Coating and Rough Coating, were considered the main contributors of the amount of investigations.

Data Analyzed on Figure 9 show that the 63.6% percent of pans impacted were manufactured in room 40D and 36.4% were manufactured in room 40A. Since the largest volume of Tablets and Caplets is manufactured in Rooms 40A and 40D. the Pareto analysis was focused on these two rooms.

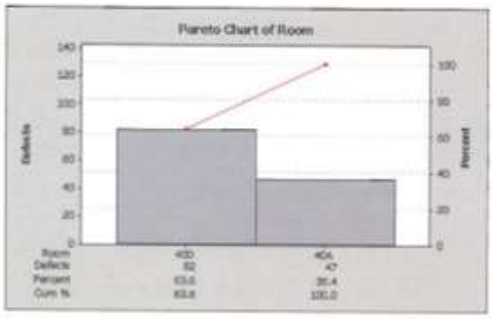


Figure 9
Percent (%) of Pan impacted by Room

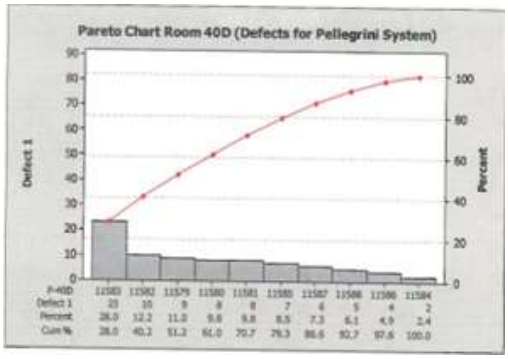
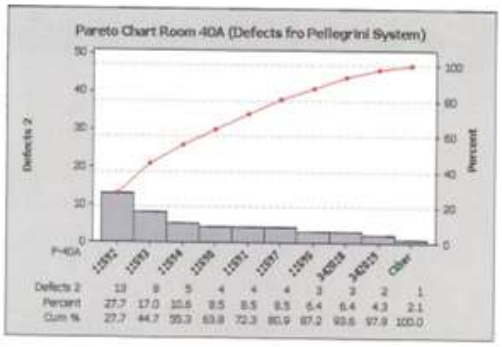


Figure 10
Percent (%) of Pan impacted by Pellegrini System located in Room 40D

As illustrated in Figure 10 presented above, the highest incidence of pans rejection and/or inspection was produced in Pellegrini system no. 11583.



Note: Other – less than 5% are distributed between pans 11596 and 11589.

Figure 11
Percent (%) of Pan impacted by Pellegrini System located in Room 40A

Based on data presented in Figure 11 presented above, the highest incidence of pans rejection and/or inspection was produced in Pellegrini system no. 11592.

Analysis Phase Conclusion

In conclusion the analysis phase provided the necessary information to determine the following:

- Color Blotches. Rough Coating, Bump on Coating, and Odd Shape were considered the main contributors of pans rejections in the coating area.
- Pellegrini System 11592 (room 40A) and 11583 (room 40D) cause a 28% of pans impacted during the period of 2020 for Tablets and Caplets.
- Three (3) areas were identified to be improved as part of Fishbone and FMEA analysis. These areas are:
    - Method - Standardization of the criteria used in the manufacturing area and QC release laboratory to determine the acceptability of the following conditions: Color Blotches, Bump on Coating, Rough Coating, Lack of Gloss, and Pits on Tablets.
    - Personnel - To develop guidelines and train personnel to identify and prevent conditions related to equipment performance during the sugar-coating process.
    - Equipment - Equipment upgrades were identified to reduce variability in the airflow volume (inlet & exhaust), air temperature, and solution application during the sugar-coating process.

Improve Phase

To implement actions for optimizing process control to consistently produce tablets/caplets with acceptable appearance the recommendations were classified using the four (4) corners approach in two (2) categories: Effectiveness and Complexity.

Based on the magnitude of the effort and expected effectiveness, the improvements identified were classified as follows: Level one (Low Effort) that capture all improvement classified as Quick Wins (I) and Short Hand Improvements (III) and Level two (High Effort) that capture all

improvements classified as Long Term Improvements (II) and Delighters (IV).

Equipment Improvements

Variability on the solution application, air flow and air temperature can influence the quantity of cosmetic conditions. Therefore, the equipment improvements were focused in these three major areas: solution application, temperature and air flow related devices.

Solution Application

Solution pumps for all rooms 40A, 40D and 40G were rebuilt. Seals and bearings were replaced for all sugar coating pumps in the three (3) rooms, during the shutdown activities of December 2020. This work optimized the solution delivery to consistently applies to the tablets.

Air pressure regulators for solution holding tank pneumatic mixers were replaced on December 2020. The solution tank mixers are powered using compressed air. Any leaks and obstruction in the air devices will affect the mixer performance. The air pressure regulators that feed the compressed air into the mixer were found with leaks and obstruction. These regulators were replaced and as a result the mixers performance improved, avoiding mixers malfunctions and interruptions.

Solution hoses for all pans were replaced by new hoses, same type, on December 2020. This also improved solution delivery performance.

Solution Tank mixers lengths were standardized to 26-% inches (Aug-2021). This is the maximum length possible without having contact with the bottom of the tank.

Temperature

Temperature parameter is controlled by supplying steam through a coil, exchanging heat with the air stream. The steam serves as the heat source and is controlled by the steam control valve. Steam control valves were verified, and specific valves were replaced or repaired as they were found stuck. When the valves are stuck, the control for the temperature parameter is affected. This fixing or replacement assure the proper control temperature in the air stream.

Air Flow

A tight limit was established for the Damper Calibration in the Sugar Coating Rooms. This calibration is performed in a weekly basis. For Room 40A, the full air flow is verified against the Mass Flow meter located at the pan inlet duct. A tightened limit was established in the full air calibration and adjustment is required when the airflow is below this limit. For sugar coating rooms 40D and 40G, the limit for the air flow measured by the pitot tube located at the inlet duct was also tightened. These changes were implemented in September 2021.

To maintain sustainability PM Maintenance Plan 78773, covers for the verification of the coating tanks, application pumps, spray guns, heat exchangers, inlet and exhaust system.

Control Reference Samples Implementation Method

Abbreviated Protocol was designed to establish guidelines to conduct a visual evaluation when tablets condition as color blotches, bumps on coating, rough coating, pits, and lack of gloss are observed after the coating process. In addition, this improvement will be used to standardize the aesthetic quality evaluation of tablets/caplets between manufacturing and QC laboratory areas. The implementation of this improvement was completed on January 2021.

Special training module was developed to qualify the manufacturing operator and QC analysts using the control samples as instructed in the abbreviated protocol. This training was used as a complement to abbreviated protocol execution to standardize criteria for cosmetic tablets evaluation and to define the minimum tablets condition appearance acceptable.

MIR Trigger Criteria

Position paper approved on December 2020 was issued to establish guidance when

manufacturing area detects aesthetic conditions that will lead to pans rejections or inspection. The position paper provides instructions of how inspection or in-process rejection will be managed in the manufacturing area. Also, procedure was issued to provide instructions that will be followed when conditions associated to the coating process are found.

Potential Improvements Identified

The following activities were initially identified as part of the brainstorm analysis, as potential improvements to control the amount of pans inspected or rejected caused by aesthetical conditions on tablets/caplets:

Control Phase

The following initiatives were implemented in the analgesic area between December 2020 to February 2021:

- Mechanical Improvements (Pump rebuilt, steam valve and regulators replacement, mixer air regulator replacement) – Implemented
- Control Samples – Implemented
- Position Paper – Implemented
- Special Training - Implemented

The coating process has been monitored to assess the effect of these actions the amount evaluates the amount of pans inspected and/or rejected in the analgesics area.

The data on Figure 12 show that the amounts of pans impacted for Tablets during the period of 2021 was reduced when compared with results for 2020. In room 40A the data at the first half of the year was observed in an increasing tendency. After implementing a tightened air flow verification during the second half of the year an improvement was observed.

The data show that the amounts of pans impacted (inspected and/or rejected) for Caplets during the period of 2020 was higher when compared with results for 2021.

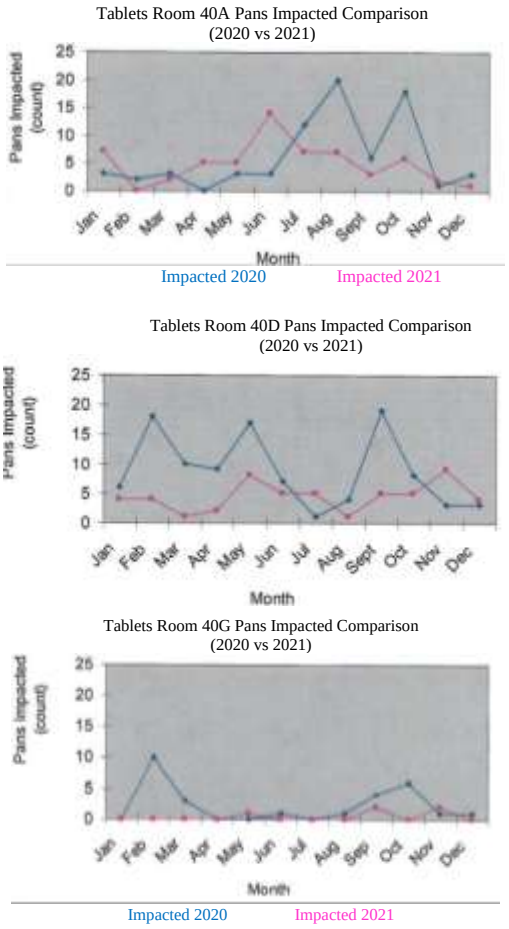


Figure 12
Tablet Pans Impacted by Room 2020 vs 2021

Therefore, the equipment improvements categorized as Solution Application, Air Flow Control and Temperature Control. Solution pumps were rebuilt for all pumps in rooms 40A, 40D and 40G. Seals and bearings were replaced for all sugars coating pumps in the three (3) rooms. Air pressure regulators of solution tank pneumatic mixers were replaced, and length of stirrers were standardized to 26- ¼ inches improving the mixers performance. Solution hoses for all pans were replaced improving the solution delivery performance.

For the Temperature Control, steam valves and pressure regulators were replaced optimizing the temperature control.

The Air Flow control was improved tightening the airflow limit established for the Damper Calibration in the Sugar Coating Rooms 40A, 40D

and 40G. The calibration is performed in a weekly basis and it assure optimum performance of the air flow.

To maintain sustainability PM Maintenance covers the verification of the coating tanks, application pumps, spray guns, heat exchangers, in let and exhaust system.

As part of method evaluation to optimize detectability, AQL standards were developed and designed to identify the acceptable tablets appearance. The standard was prepared in duplicate, one (1) for the manufacturing area and one (1) for the Quality Control Laboratory.

As part of the personnel evaluation, a special training was deployed to operators. This course was designed to enhance the skills to identify and prevent product not meeting acceptable appearance in the sugar-coating area.

As a result of these improvements, the rejection of pan produced was reduced as mentioned above and the goal of the project was attained.

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