Coating Process Improvements in Solid Dose Form Manufacturing

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Abstract *— Organization's goals and objectives use strategic scorecards that include Quality, Economics, Speed and Culture to establish business metrics focused on building continuous future success and competitiveness to create value. As a result, manufacturing facilities are encouraged to adopt Lean Transformation to align to an organization's priorities and goals. Assessments of the manufacturing processes in a single dose manufacturing facility and interviews with key personnel to determine potential opportunities were performed by means of Voice of the Costumer. Cycle Time Reduction for Color Suspension and Clear Solution Preparation was attained with a minor equipment modification that improved material reconstitution minimizing mixing time, air entrapment and foaming formation; thereby, reducing the deaeration time. Cycle Time Reduction for Line Flush was achieved by increasing (2X) USP Purified Water flow rate. Spray Gun Performance using an equivalence test between Pan Loads, Manufacturing controls and procedures evaluation and standardization of spray guns assembly supported the reduction of spray gun verification frequency. Removal of redundant documentation where automated systems are in place and verifications by a second person from non critical steps according to 21 CFR Part 211 Subpart F--Production and Process Controls reduced redundant documentation and head count. A 62% cycle time reduction (6.91 hrs hours from 11.4 hrs) per lot as well as 1 head count reduction ($43,680) were the immediate benefits attained from all process improvements.*

Key Terms *— Critical to Quality (CTQs), Cycle Time, Voice of the Costumer (VOC), Waste, Coating Improvement, Solid Dosage Forms.*

INTRODUCTION

Manufacturing facility dedicated for a single solid dose drug product manufacture which involves the following unit operations:

- Weighing and dispensing
- Granulation: three (3) sub lots individually processed in a high shear granulator, wet milling, fluid bed drying, dry milling and collected together in an Intermediate Bulk Container.
- Blending: Pre-blending and lubrication steps are performed to achieve a theoretical target for the final lubricated granulation blend.
- Compression
- Film coating (three pan loads): color suspension, clear solution and wax application.

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The Film Coating Process was identified as the bottleneck of manufacturing process. Process Cycle Time as well as redundant procedural and documentation practices are identified sources of waste. Cycle Time is the frequency that a part/product is completed by process. Also, time it takes for operator to go through work activities before repeating the activities [1].

Lean tools such as Voice of the Costumer (VOC) and the identification of sources of waste facilitated the identification of areas of improvement in the Coating Process. Voice of the Costumer (VOC) refers to the range of results that are acceptable to a costumer, whether in a numeric specification or verbal feedback [2]. Waste is the seven elements to consider for the elimination of muda (a Japanese term for waste) which are correction, overproduction, processing, conveyance, inventory, motion and waiting [3].

Areas of improvement identified include: (1) Color Suspension and Clear Solution Preparation (2) Line Flushing Step, (3) Spray Gun Verification and (4) Reduction of process data recording and verification.

FILM COATING PROCESS OVERVIEW

Color and Clear Coating Preparation

Film coating entails the subdivision of uncoated tablets lot into three (3) pan load portions. The color suspension preparation and the clear solution use independent mixing tanks equipped with an agitator. Figure 1 presents the Color Suspension and Clear Solution Equipment Train.

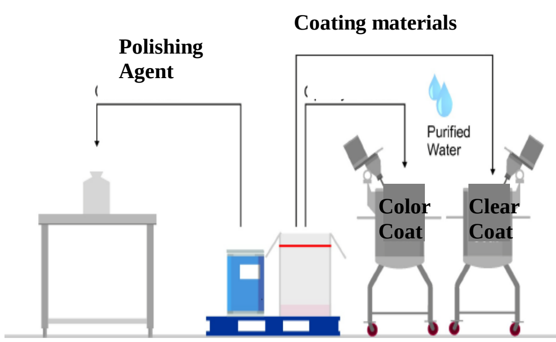


Figure 1
Color and Clear Coating Equipment Train

For the color suspension preparation, the color film material is slowly added over a period of 15 ± 5 minutes at an agitator speed setting of 310 rpm (300 – 320 rpm range) into USP Purified Water to prevent clump formation.

The color suspension material is mixed for no less than 45 minutes at 250 rpm (240 – 260 rpm range), followed by a de-aeration step for a minimum of 250 minutes (4.17 hours) at a speed setting of 80 rpm (70 - 90 rpm range) prior to use in the film-coating application steps. Table 1 summarizes color suspension preparation process parameters.

Table 1
Color Suspension Preparation

Process Step	Time (MIN)	Speed (RPM)
Material Addition	10 – 20	310 (300-320)
Mixing	NLT 45	250 (240-260)
Deaeration	NLT 250	80 (70-90)

For the clear solution preparation, the clear film material is slowly added over a period of 15 ± 5 minutes at an agitator speed setting of 290 rpm (280 – 300 rpm range) into USP Purified Water to prevent clump formation. The clear solution is mixed for no less than 45 minutes at 210 rpm (200 – 220 rpm range), followed by a de-aeration step for a minimum 250 minutes at a speed setting of 40 rpm (30 - 50 rpm range) prior to use in the film-coating application steps. Table 2 summarizes clear solution preparation process parameters.

Table 2
Clear Solution Preparation

Process Step	Time (MIN)	Speed (RPM)
Material Addition	10 - 20	290 (280 – 300)
Mixing	NLT 45	210 (200-220)
Deaeration	NLT 250	40 (30-50)

Spray Gun Verification

Film coating process consists of the color suspension and clear solution application onto a dynamic uncoated tablet bed rotating in the pan drum at a constant spray rate in an Accela-Cota 48" Coater.

The Accela Cota 48" spray gun manifold has 4 spray guns. Spray guns are used in the film coating process to distribute the coating suspension/solution on tablet bed to achieve a uniform distribution of liquid onto the surface of every tablet. The color suspension and clear solution pass through a 60-mesh strainer installed on the solution delivery line to the spray gun manifold. The peristaltic pump delivers the color suspension and clear solution at a defined flow-rate measured by the in-line flow meter. Each manufacturing lot consists of three (3) pan loads; as a result, a total of three (3) spray gun verifications are performed per lot manufacture.

The spray gun verification test is performed manually by opening the pan drum door and swinging out the coating solution delivery manifold to the right of the pan with graduated cylinders for collection of the color suspension during the test before each pan load coating. The target flow rate of 310 g/min (range of 260-360 g/min) is used to perform the verification test, and the individual values collected from each of the spray guns after 1 minute are recorded in the Manufacturing Procedure. The corresponding target value for each of the four guns is 77.5 g/min (acceptable range of 65-90 g/min) and is used to verify that flow rate is within range prior to start the film-coating process. Once the spray rate verification is completed, Compu Coat 6 records ongoing process parameters including spray rate throughout the process and reported in the Compu-Coat 6 Periodic Data Subreport every sixty (60) seconds.

Color and Clear Coating Application Process

Each pan load is coated with a color suspension and clear solution in an Accela-Cota 48” Coater (3 pan loads per lot). Figure 2 presents the Coating Process Equipment Train.

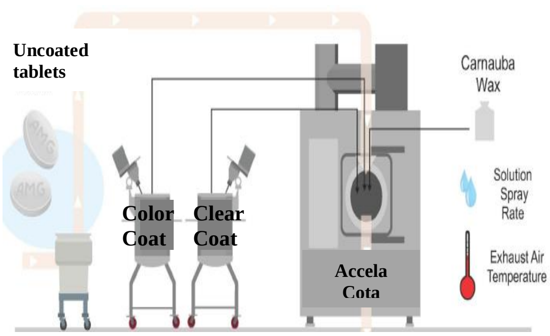


Figure 2
Coating Equipment Train

The color-coating suspension is applied at a constant spray rate of 310 g/min onto a dynamic uncoated tablet bed rotating in the pan drum. After the complete amount of color suspension is applied, a line flush with USP purified water and a prime with Clear solution is performed to remove the color suspension from the solution line, then, the clear coat is applied. Solution lines flush time is 30 minutes theoretically and up to 40 minutes during actual operation.

When the clear-coating application is completed, a polishing agent is evenly added to the moving tablet bed and tablets are cooled down before discharge. Table 3 summarizes Line Flush process parameters.

Table 3
Line Flush Parameters

Parameter	Target Value
Stage Time (sec)	1800
Solution Flow rate Setpoint (g/min)	310
Solution Flow rate Hi Alarm (g/min)	360
Solution Flow rate Low Alarm (g/min)	260

PROBLEM STATEMENT

New manufacturing facility for the commercial manufacture of small molecules (solid oral dosage forms) since 2011 involves: Weighing/Dispensing, Wet Granulation, Wet Milling, Fluid Bed Drying, Dry Milling, Blending, Compression and Film Coating. Key stakeholders identified the Film Coating Process as the bottleneck of manufacturing process.

Film coating process operates in 2 shifts of 8 working hours. Color suspension and clear solution preparation and application takes up to 3 shifts with a solution hold time of 24 hours.

A minimum of 2 manufacturing associates are required per unit operation to comply with GMP documentation requirements.

Consequently, manufacturing standard work planning and personnel flexibility are a continuous challenge. The goal of this project is to decrease Coating Process Cycle Time 40% per lot by minimizing identified sources of waste in the process.

METHODOLOGY

DMAIC (Define-Measure-Analyze-Improve-Control) problem-solving methodology was followed to define the problem, implement solutions associated to underlying causes, and establish best practices to ensure the solutions stay in place [3].

Define Phase objective was to agree with the costumer the problem definition, project scope, performance goals and plan. A SIPOC diagram was used to illustrate the current Coating Process and work with the "Customers" to develop the detailed requirements [3]. Coating Process manufacturing controls, procedures, equipment set up, dynamic process and GMP documentation practices were evaluated. Voice of the Costumer (VOC) was captured by direct discussions/interview with the internal client. Manufacturing personnel needs were defined into specific critical-to-quality requirements (CTQs). Critical to Quality (CTQs) are the internal critical parameters that relate to the wants and needs of the costumer [3].

Measure Phase objective was to understand the current state of the process also known as the baseline. A Waste Walk identified process steps that add no value from the costumer's point of view. A Control Chart was used to determine the Coating Process Cycle Time baseline.

Analyze Phase objective was to identify how the input factor (X's) of the process affect the output (Y's) significantly. A Cause and Effect Diagram was use as a problem solving tool to identify potential root causes for coating process efficiency reduction.

Improve Phase objective was to make changes in the process X's to improve the outputs (Y's). Potential solutions to identified process deficiencies were implemented. Pilot Study was executed to document supporting evidence of the solution effectiveness prior to implementation.

Control Phase objective was to establish mechanisms or processes that sustain cycle time and head count reduction.

RESULTS AND DISCUSSIONS

Define Phase: An overview of the process presented in a SIPOC diagram defines the Coating Process as the project's scope and boundaries starting with equipment setup and ending with polishing agent application. Out of scope are the Granulation and Compression Processes. Figure 3 presents the SIPOC Diagram.

Manufacturing personnel provided feedback to determine potential opportunities to improve current process state. Cycle time reduction in film coating preparation and line flushing, reduction in spray gun verification frequency and data recording simplification were the identified costumer needs. Figure 4 presents CTQ Tree.

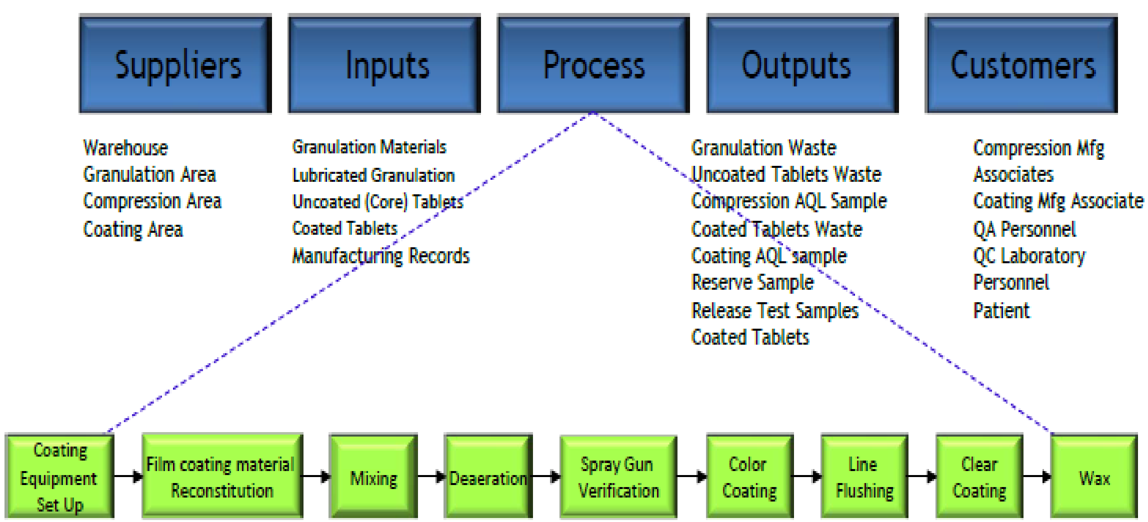


Figure 3
SIPOC Diagram

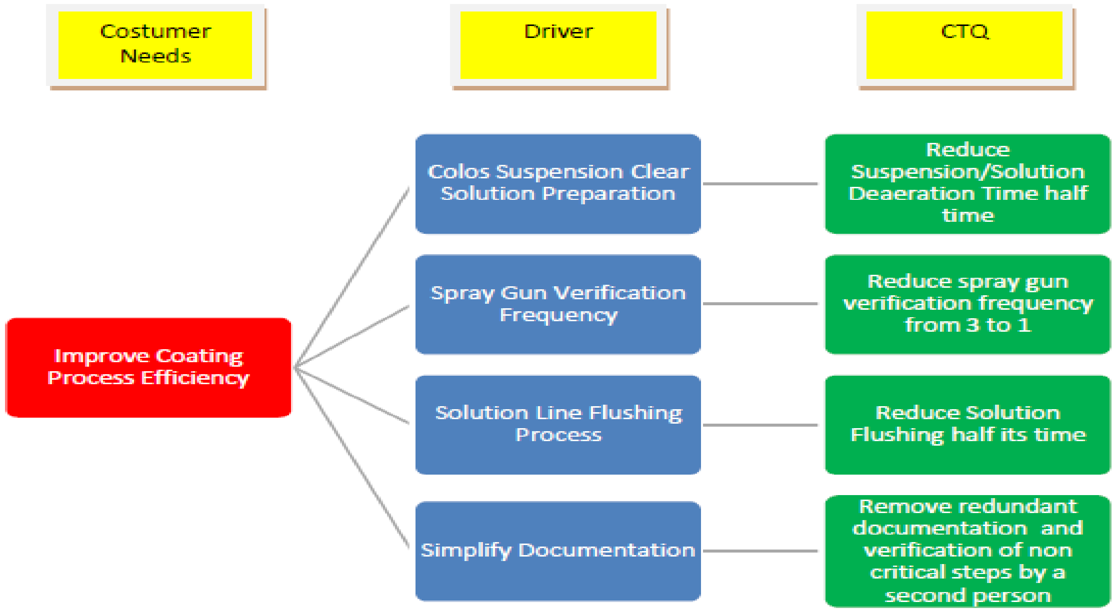


Figure 4
CTQ Tree

Measure Phase: A Visual detailed representation of the process also known as Waste Walk identified the Suspension/Solution Preparation, Spray Gun Verification, Line Flushing and Documentation as over-processing wastes. Figure 5 presents the Waste Walk for the Coating Process.

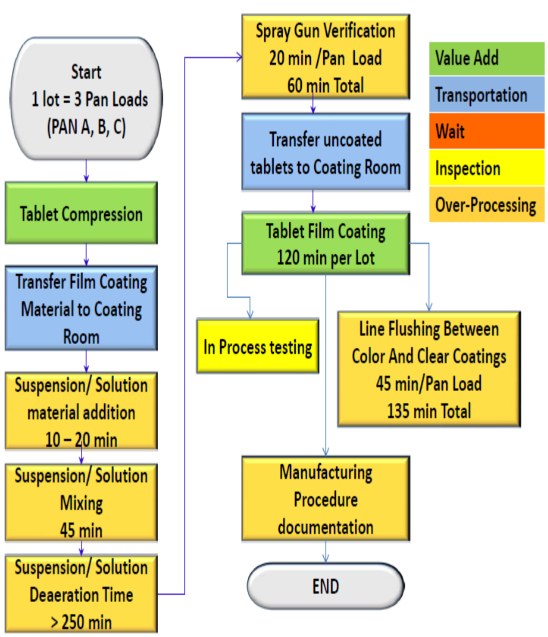


Figure 5
Waste Walk

Suspension and solution preparation time that includes material addition, mixing and deaeration time is NLT 6 hrs (360 min) per lot.

Spray Gun Verification is performed in manual mode using the color suspension prior to start the coating process each pan load (Pan A, B and C). Each manufacturing lot consists of three (3) pan loads; as a result a total of three (3) spray gun verifications are performed per manufacturing lot. Spray gun verification takes up to 20 minutes per pan load for a total of 60 minutes per lot.

Solution lines flush time takes approximately 135 minutes per lot (30 minutes theoretically and up to 45 minutes during actual coating operation per pan load). Figure 6 presents Control Chart for Film Coating Cycle Time. An overall baseline cycle time of 684 minutes (11.4 hours) is defined as the baseline for the Film Coating Application.

The color suspension and clear solution application process are continually monitored with manual (Master Batch Record) and automated (Compu-Coat 6) documentation of key and critical operational parameters generating redundant data records.

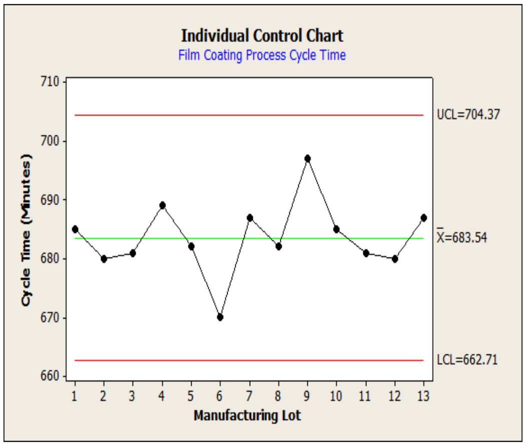


Figure 6
Individual Control Chart

Analyze Phase: A Cause and Effect Diagram identified procedural improvements for solution/suspension preparation, equipment modification, spray gun verification, line flushing and documentation as potential root causes for coating process efficiency reduction. Figure 7 presents the Cause and Effect Diagram of Coating Process Efficiency Reduction.

Color Suspension and clear solution parameters and impeller size and location increase foaming and air entrapment during the mixing process. Film coating material addition rate of 15 ± 5 minutes modification is required to attain a more efficient powder dissolving process/method to minimize foam formation.

The expected outcome is a suspension and solution de-aeration time from not less than 250 minutes to the lowest attainable time.

Spray Gun verification is performed prior to start the coating process for each pan load (Pan A, B, C) following a conservative approach. No non conformances have been associated to spray gun performance.

Coating process parameters documentation redundancy results in data over processing. Due to manufacturing procedure requirements, no less than 2 operators are required to be present during execution of critical and non critical steps in the Compression Process.

Improve Phase: Potential solutions to identified process deficiencies were implemented to minimize process cycle time, eliminate documentation redundancy and reduce head count.

Suspension and Solution Preparation Improvement: Agitators' location and dimension were determined to standardize equipment assembly. The current Agitator A and Agitator B shafts length 33" with impellers length 10" each, were replaced by Agitators with shafts length 35¼" each (nominal value) with impellers length 10" each to allow placement of the impeller closer to the bottom of the tank to deepen the vortex formation.

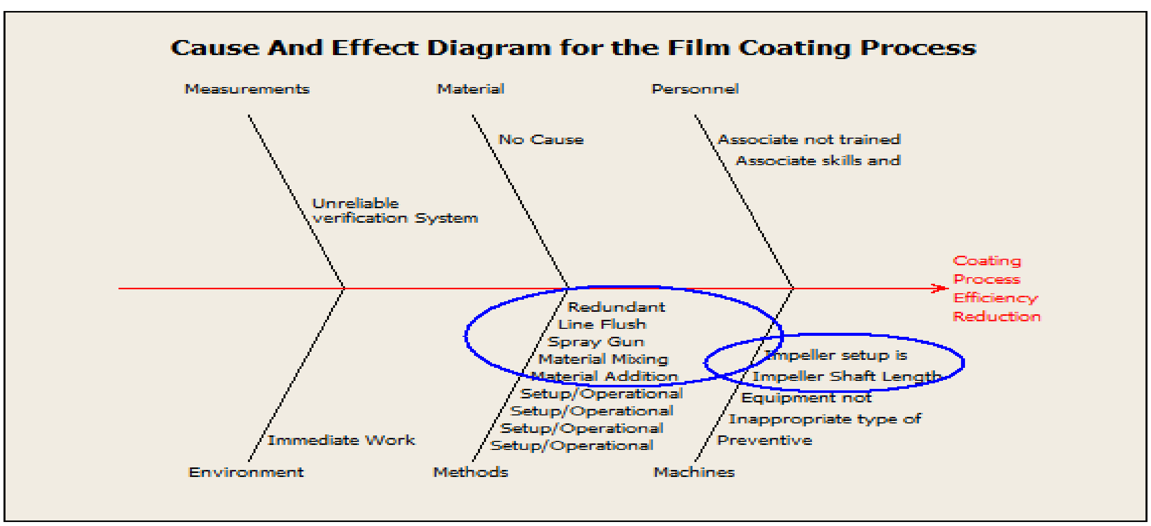
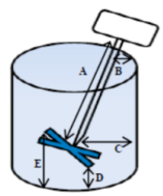


Figure 7
Cause and Effect Diagram

Once installed, the impeller's shaft working length is 30" each. Figure 8 presents Impellers Dimensions.

Impellers (35¼") Location Dimensions



Location	Agitator A Distance (in)	Agitator B Distance (in)
A. Shaft Working Length-mounted (Shaft's top to impeller's top)	30	30
B. Shaft's top to tank's top side border	2 ¾	2 ¾
C. Shaft bottom to tank's bottom side.	10 ¼	10 ¼
D. Impeller's shaft lowest point to the bottom of the tank	2 ¼	2 ¼
E. Impeller's shaft highest point to the bottom of the tank	5	5

Figure 8
New Impellers Dimensions

A pilot run was executed to demonstrate the equipment part modification effectiveness. The increase in the impeller shaft length from 33" to 35¼" placed the impeller blades closer to the bottom of the tank deepening the vortex formation. As a result, the larger (pronounced) vortex surface area improved material reconstitution with USP Purified Water minimizing mixing time, air entrapment and foaming formation; thereby, reducing the deaeration time.

Due to the larger surface area created by the pronounced vortex the suspension and solution preparation method was modified. The addition rate of Color and Clear materials was reduced from (10-20) min to (10-15) min. Table 4 presents pilot run results for film coating material.

Preparation mixing time was reduced from NLT 45 minutes to 30 minutes for color material and 38 minutes for clear material. Table 5 presents pilot run results for film coating material mixing step.

Table 4
Film Material Addition Modification

Stage	Process Parameter	Actual	Pilot Run
Color Suspension Preparation	Time (min)	15 (10 – 20)	11
	Speed (RPM)	310 (300-320)	300 (290-310)
Clear Solution Preparation	Time (min)	15 (10 – 20)	10
	Speed (RPM)	290(280-300)	290(280-300)

Table 5
Film Material Mixing Modification

Stage	Process Parameter	Actual	Pilot Run
Color Suspension Mixing	Time (min)	NLT 45	30
	Speed (RPM)	250 (240-260)	250 (240-260)
Clear Solution Mixing	Time (min)	NLT 45	38
	Speed (RPM)	210 (200-220)	210 (200-220)

Upon initiation of the deaeration step, approximately 2 inches of foam formation were observed. The amount of foam generated differs from the validated process which generates approximately 5"-6" of foam. Foam formation in the surface of the suspension is an inherent process characteristic which results from the release of entrapped air within the suspension generated during mixing process. The color suspension and clear solution de-aeration time was reduced from NLT 250 minutes to NLT 150 min due to reduced foaming formation during mixing. Table 6 presents pilot run results for deaeration step. Suspension and solution cycle time was reduced from 360 min (6 hrs) to 215 min (3.5 hrs).

Table 6
Film Material Deaeration Modification

Stage	Process Parameter	Actual	Pilot Run
Color Suspension Mixing	Time (min)	NLT 250	150
	Speed (RPM)	80 (70-90)	40 (30-50)
Clear Solution Mixing	Time (min)	NLT 250	150
	Speed (RPM)	40 (30-50)	35 (25-45)

Spray Gun Verification Improvement: Spray gun verification frequency reduction was based on the evaluation of actual spray gun performance maintained throughout the coating process and actual process controls. Homogeneity (Equivalence) of spray gun performance was determined across pan loads A, B and C of seven (7) manufacturing lots for a total of twenty-one (21) data sets. The main objective of the average difference equivalency approach was to test the null hypothesis of non-equivalence (i.e. heterogeneity). If the null hypothesis is rejected then evidence of equivalence (i.e. homogeneity) is demonstrated. The three comparisons must be within the equivalency acceptance criterion of two times the upper bound of the 95% confidence interval of Pan A standard deviation (Lower Limit -2.29661, Upper Limit 2.29661) to demonstrate equivalence within lot.

Solution Flow rate (g/min) data evaluation of twenty-one (21) pan loads demonstrates that satisfactory spray gun performance is maintained throughout the coating process (Pan A,B,C) with no process interventions once the initial gun verification (Pan A) is performed. It was also demonstrated that current process controls are deemed adequate to maintain a consistent spray gun performance. Table 7 presents the results equivalence test of one lot evaluated.

Process variables serve as indicators of current process condition. Pan variables affect the mixing of the pan load. Process air variables are controlled to obtain an optimum drying setting. Spray variables such as spray rate, degree of atomization and spray pattern are affected by fluid pressure and nozzle design. The afore mentioned variables are monitored as part of the coating process to maintain process control. Spray gun verification frequency was reduced from 3 to 1verification per lot with a cycle time reduction from 60 min to 20 min.

Table 7
Equivalence Test Result

Comparison	Reference	Confidence Interval for Difference		Equivalence Test Conclusion
		Lower	Upper	
A-B	A	-0.1894	0.3492	Pass
B-C	B	-0.3909	0.1391	Pass
C-A	C	-0.2179	0.3097	Pass

Solution Flush Line Improvement: To reduce flush time, the solution flow rate was increased from 310 g/min to 620 g/min. A pilot run was performed to determine the lowest attainable time to flush the color suspension from the solution lines. The test criterion was absence of the color suspension at the recirculation port. Total flush time attained from the 3 runs ranged from 16 up to 20 minutes. The difference in flush times was observed due to system alarms. Flush time was reduced from 135 min to 60 minutes per pan load.

Documentation Improvement: Manufacturing Batch Records were modified to remove documentation collected by automated system and the requirement of second person verification from non-critical steps. Second person verification requirement was maintained for critical steps such as material addition. Documentation changes were performed in alignment with 21 CFR Part 211 Subpart F-Production and Process Controls [4].

Implementation resulted in cycle time reduction from 684 min. (11.4 hrs) to 425 min. (7.1 hrs), elimination of redundant data and one head count reduction ($43,680). Figure 9 presents the coating process cycle time reduction.

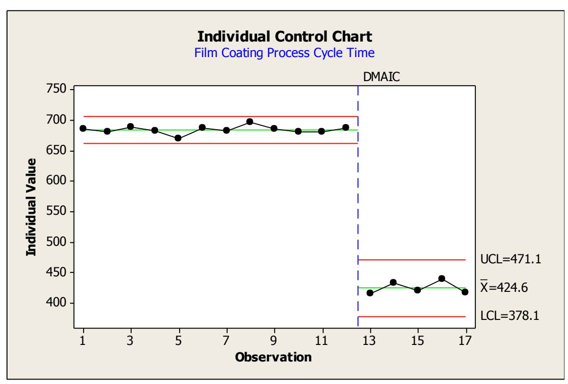


Figure 9
Coating Process Cycle Time Reduction

Control Phase: Based on the Pilot Run results for the Suspension and Solution preparation process, the standard operating procedure was revised to define Agitator A and Agitator B location and dimensions in relation to the tank's top, side and bottom walls to standardize equipment assembly. Manufacturing Batch Records and procedures were revised to include new material addition, mixing and deaeration parameters, modify the spray gun instruction to perform a single verification prior to start the first pan load (Pan A) and re-in force current process controls including instructions for the disassembly/assembly of Schlick spray gun and nozzle clean up prior to start the coating process of each pan load. The coating recipe was modified to decrease the solution line flush stage time from 1800 seconds to 900 seconds and increase Solution Flow Rate Set Point to 620 g/min. Manufacturing procedures were revised to remove steps related to redundant documentation and verifications by a second operator from non critical steps.

CONCLUSION

Coating process improvements were identified and accomplishing using the Six Sigma DMAIC methodology in a way that is systematic, sustainable, confirmed with data, and in alignment with customer and stakeholder quality expectations. Results confirmed adequacy of recommended process improvements. Equipment modification reduced the suspension/solution reconstitution time, mixing time, foaming formation and de-areation time. Increasing flow rate during line flushing reduced actual flush time. Equivalence test supported the reduction of the spray gun verification. Benefits from implementation of all process improvements include a 62% overall cycle time reduction from 684 min (11.4 hrs) to 425 min (7.1 hrs), elimination of redundant data and one head count reduction ($43,680) in gained benefits.

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REFERENCES

[1] Breyfogle III, F. W. (2003). *Implementing Six Sigma Smarter Solutions® Using Statistical Methods.* Hoboken, New Jersey, pp. 1104

[2] Brook, Q. (2005). *Lean Six Sigma & Minitab® The Complete Toolbox Guide for all Lean Six Sigma Practitioners,* pp. 1-26, 56-57

[3] George, M. Rowlands, D. Price,M. , Maxey, J. (2005). *The Lean Six Sigma Pocket Toolbook, New York, pp.* 1, 38, 55

[4] Title 21 Part 211. (2013). *Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart F--Production and Process Controls*