Application of Design of Experiment to Demonstrate Equivalency of Two Multi Layer Compression Process for an Extended Release Tablets Product

Jaime Carrión Vega
Manufacturing Engineering
Rafael Nieves, Pharm. D.
Industrial Engineering Department
Polytechnic University of Puerto Rico

***Abstract* —** *A design of experiment (DOE) was performed to a multi layer compression process that is going to be transferred from facility A to facility B. This study demonstrates and compared the equivalence of the compression process of a non-validated process site with a validated process from the original site. The relevance of this project is to demonstrate the equivalence of the process to ensure the robustness, and quality of the product. During the compression process, the weight of multiple stages, thickness, and hardness were collected in both machine. The data collected was analyzed using One-Way-ANOVA and Kruskal-Wallis test. Based on the results obtained from the data, it was concluded that both multi layer compression process are equivalent.*

***Key Terms* —** *Design of Experiment, Extended Release Tablets, Multi Layer Compression Process, One – Way – ANOVA.*

INTRODUCTION

Design of experiment (DOE) is a statistical tool used in the industry to improve or develop a manufacturing process [4]. As a result the quality of the product improves to better performance and reliability. Also, design of experiment can be used to develop a product in less time, contributing in reducing the associated cost of development.

Process validation is one of the requirements that have to be met under the Food and Drug Administration (FDA) [2]. Design of experiment is one of the tools that can be used to meet the requirements to validate a process. "An experimental design is a series of statistically sufficient qualification trials that are planned in a specific arrangement and include all processing variables that can possibly affect the expected outcome of the process under investigation" [1]. Subsequent experiments are used to refine this information and determine which adjustments to these critical variables are required to improve the process [4].

The objective of the experimenter is optimization. That is, to determine which levels of the critical variables result in the best process performance [4]. As a statistical tool it is used in the engineering field for making a decision in a process to:

- Develop a new process.
- Improve a manufacturing process.
- Determine critical variables o parameters.
- Reduce operational cost.
- Evaluate different materials.
- Evaluation and comparison of basic design configurations [4].

Sustained release drug is "any drug or dosage form modification that prolongs the therapeutic activity of the drug" [3]. The development of sustained release product started with Israel Lipowski in 1938. His work "was presumably the forerunner to the development of the coated-particle approach to sustained drug delivery that was introduced in the early 1950s" [3].

The mechanism use for the product X being analyzed in this project is osmosis. Osmosis consists of a semipermeable membrane around a Tablet that creates an osmotic pressure that helps to pump the drug solution out of the Tablet through a small orifice in the coat. The key component of the system is the ability of a drug solution to attract water through a semipermeable membrane by osmosis [3].

The product X being analyzed is made of a Tablet of three layers and an orifice. Each layer has a specific function in the Tablet (Figure 1).

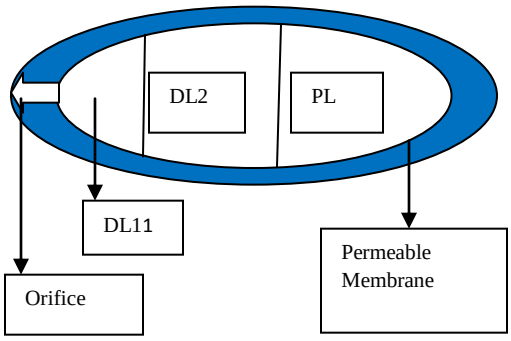

Figure 1
Three layer Tablet (Product X) representation

Layer one is called push layer (PL). The PL is made of a material that will expand when it is exposed to a liquid. The expandable material it is exposed to liquids through a membrane that covers the hole Tablet and, this membrane use the osmosis mechanism to expand the material of layer one. This expansion will help release the active ingredient of the Tablet. Layer two is called drug layer two (DL2). DL2 contains the active ingredient that is going to be push by the PL through a small orifice that contains the Tablet. DL2 will be releasing the active ingredient on a sustainable manner. Layer three is called drug layer one (DL1). DL1 contains the active ingredient that is going to be released immediately through a small orifice that contains the Table. DL1 will be push also by the PL.

There are nine steps in the manufacture process of Product X that has the mechanism of sustained release drug. The following flow chart describes the manufacturing process of Product X, as presented in Figure 2.

The Tablet press machine used to form the three layer Tablet was a Korsch TRP-900 (refer to Figure 2) multi layer Tableting press machine (MLTPM). The machine consists of sixty seven (67) stations and it has five filling compression stages. However, only three filling compression stages were used.

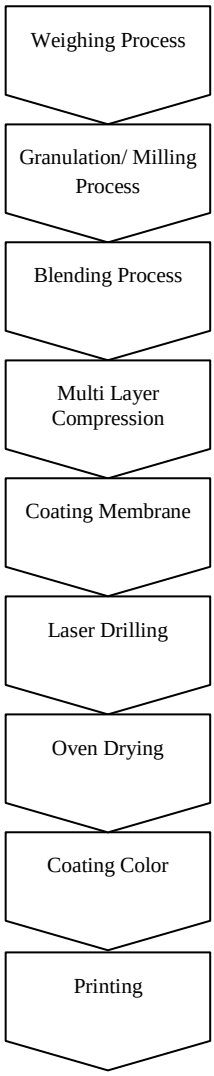

Figure 2
Process Flow Chart of the manufacture of Product X

The Korsch provide independent control for each layer weight. This machine includes peripherals equipment which is a Tablet deduster, a metal detection device, a Tablet collection system, and a Tablet sampling unit. The machine has a capacity to produce 5,360 Tablets per minutes. The Korsch is built on a modular control design on Siemens PLC platform, diagnosis monitoring system, and SCADA system. The first stage is where the PL is form by filling the die with the PL material then, compressing the PL material with the upper and lower punches. The second stage is the

DL2 material, is added by filling the same die where the PL material is. An amount of compression force is exerted to both layer with an upper and a lower punches. After the compression force is exerted, a two layer Tablet is form. The third stage is the DL1, is added by filling the same die were the PL material and the DL2 are. A final compression force is exerted to the three layer Tablet. Then the three layer Tablet is ejected outside the die by the lower punch elevating the Tablet and using a knock-off plate to eject the Tablet outside the die.

Figure 3
Korch TRP-900

METHODOLOGY

In this section summarize the methodology used to do the experiment and analysis of the data obtained.

- Determination of the factors or variables that impact the output of the process.
- Determination of the number of levels or condition for each identified factor.
- Selection of response variables. The response variable was the output of the process.
- Creation of the design of experiment.
- Conduction of the experiment and collection of data.
- Data analysis using statistical tools. Statgraphics Centurion XV™ (statistical program) was used to analyze the data.

RESULTS

Three validations batches processed in a MLTPM were sampled. The samples were taken at different velocities. Each batch was processed at different velocity. The first batch was processed at low velocity, the second batch was processed at medium velocity, and the third batch was processed at high velocity. Therefore, the velocity was the factor.

The three validation batches were compared with a normal validated batch processed in a MLTPM from the original site. The velocity in the normal validated batch was remained constant.

The factor of the three validations batches had three levels, which are low, medium and, high velocity, respectively. For the normal validated batch the velocity was treated also as a three level factor. However, the samples were taken randomly at different time intervals.

The variables analyzed in the process were the weight of PL, the weight of PL & DL2 weight, and the total weight of the Tablet which include PL, DL2, and DL1. Also, the thickness and the hardness of the Tablet were analyzed. The friability was not analyzed in this experiment because the parameters that are being considered were the parameters that affect directly the process operation. Also, no chemical testing was considered in this experiment. The statistical program Statgraphics Centurion XV ™ was used to create the experimental design. In this Table of data a randomize block design was considered to eliminate any nuisance source especially in the thickness variable which are measure by different operators. Also, since two processes are being compared in different conditions, the block design will eliminate any other nuisance source. For each variable a Table data of randomize block design was created.

In this experiment the equivalency of the process was established when the following condition were met:

- The equivalency of the process is true because the null hypothesis is accepted.
- The significant level was $\alpha = 0.05$, the confident level was 95.0%.
- The P-value > α: then H_0 will be accepted.
- The P-value < α: then H_1 is accepted. Under this condition the means are significantly

different and there is no proof that the two processes are equivalent.

- One Way ANOVA was the statistical tool used in this experiment to analyze the data for each response variable, since there was only one factor to be considered to compare both processes.
- The Kruskal-Wallis test was used to validate the null hypothesis.

The parameters of the compression process are in Table 1:

Table 1
Operation process parameters

Parameter	PL	PL & DL2	Total Weight
Weight mg	70.0 – 90.0	229.0 – 263.0	404.0 – 448.0
Hardness kp			13 – 35
Thickness mm			13.9 -14.9

The results obtained from the Statgraphics™ are summarize in Table 1 with $\alpha = 0.05$. One Way ANOVA is an analysis of variance of a single factor. It is a linear statistical model expressed as:

$$y_{ij} = \mu + \tau_i + \epsilon_{ij}\{i = 1,2,\ldots,a \,\&\, j = 1,2,\ldots,n\} \quad (1)$$

where ϵ is the random error, τ is the parameter of the treatment, μ is the overall mean and, y is the response variable. One way ANOVA is used to compare the mean of two different populations. If the means of a certain parameters are equal or not significantly different then H_0 is accepted. The null hypothesis is expressed as:

$$H_0: \mu_1 = \mu_2 = \ldots. = \mu_\alpha \quad (2)$$

However, if at least one of the means is not equal or significantly different then null hypothesis is rejected and the alternative hypothesis is accepted [5].

Kruskal-Wallis test provide the analysis of variance. It is a parametric method that assumes that the means follow a normal distribution. However, when the means do not follow a distribution an alternative method needs to be used to test the null hypothesis. These methods are called nonparametric methods and Kruskal-Wallis is an alternative method to test the null hypothesis because does not depend on a normal distribution assumption. It is used to test the null hypothesis in testing the equality of treatments means when the normality assumption is unjustified [5].

Table 2
Summary of Results

Parameter	ANOVA P-value	Kuskal-Wallis P-value	H_0
PL-Weight	0.8744	0.969341	Accepted
PL & DL2 Weight	0.7323	0.757356	Accepted
Total Weight	0.9913	0.942746	Accepted
Thickness	0.7530	0.822363	Accepted
Hardness	0.0948	0.16796	Accepted

Push Layer (PL) Weight

The statistical analysis for Push Layer (PL) weight (refer to Table 2) shows a P-value = 0.8744 which, is greater than $\alpha = 0.05$. The analysis indicates that there is no significant difference between the means of each level of the velocity. Therefore, the null hypothesis is accepted.

The Box and Whisker Plot graph (refer to Figure 4) indicates that the means do not have significant difference between the means of each level of the velocity.

The Kruskal Wallis test obtained a P-value = 0.969341 which it is greater than $\alpha = 0.05$. Therefore, the test validates the H_0 acceptance.

Push Layer & Drug Layer 2 (DL2) Weight

The statistical for Push Layer and Drug Layer 2 weight analysis (refer to Table 2) shows a P-value = 0.7323 which, is greater than $\alpha = 0.05$. The analysis indicates that there is no significant difference between the means of each level of the velocity. Therefore, the null hypothesis is accepted.

The Box and Whisker Plot graph (refer to Figure 5) indicates that the means do not have significant difference between the means of each

level of the velocity. The Kruskal Wallis test obtained a P-value = 0.757356 which it is greater than $\alpha = 0.05$. Therefore, the test validates the H_0 acceptance.

Total Weight

The statistical analysis for Total weight (refer to Table 2) shows a P-value = 0.9913 which, is greater than $\alpha = 0.05$. The analysis indicates that there is no significant difference between the means of each level of the velocity. Therefore, the null hypothesis is accepted.

The Box and Whisker Plot graph (refer to Figure 6) indicates that the means do not have significant difference between the means of each level of the velocity. The Kruskal Wallis test obtained a P-value = 0.942746 which it is greater than $\alpha = 0.05$. Therefore, the test validates the H_0 acceptance.

Thickness

The statistical analysis for Thickness (refer to Table 2) shows a P-value = 0.7530 which, is greater than $\alpha = 0.05$. The analysis indicates that there is no significant difference between the means of each level of the velocity. Therefore, the null hypothesis is accepted.

The Box and Whisker Plot graph (refer to Figure 7) indicates that the means do not have significant difference between the means of each level of the velocity. The Kruskal Wallis test obtained a P-value = 0.822363 which it is greater than $\alpha = 0.05$. Therefore, the test validates the H_0 acceptance.

Hardness

The statistical analysis for Hardness (refer to Table 2) shows a P-value = 0.0948 which, is greater than $\alpha = 0.05$. The analysis indicates that there is no significant difference between the means of each level of the velocity. Therefore, the null hypothesis is accepted.

The Box and Whisker Plot graph (refer to Figure 8) indicates that the means do not have significant difference between the means of each level of the velocity. However, in level 2 the hardness tendency is to be higher. This could mean that there is a probability that velocity could affect the hardness of the Tablet or, the operator that took the samples may have caused a variation. The Kruskal Wallis test obtained a P-value = 0.16796 which it is greater than $\alpha = 0.05$. Therefore, the test validates the H_0 acceptance.

Box and whisker plots are a graphical display that simultaneously describes several important features of a data set, such as centers, spread, departure from symmetry, and identification of observations that lie unusually far from the bulk of the data [4].

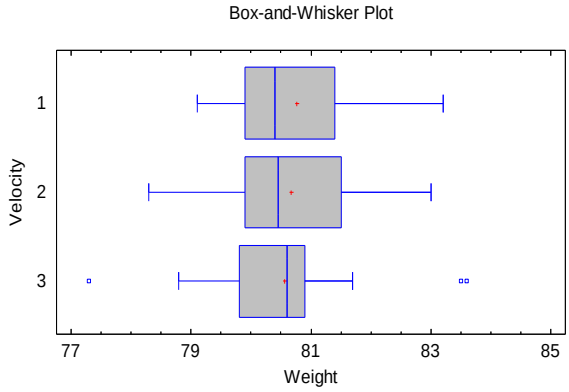

Figure 4
PL Weight vs. Tablet Press Velocity

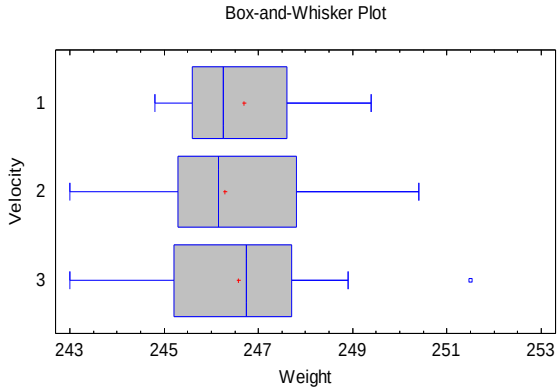

Figure 5
PL & DL2 Weight vs. Tablet Press Velocity

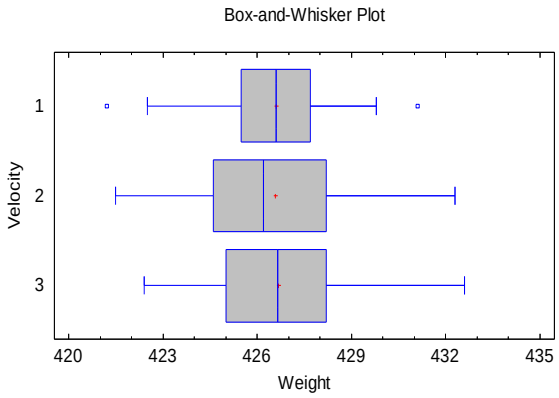

Figure 6
Total Tablet Weight vs. Tablet Press Velocity

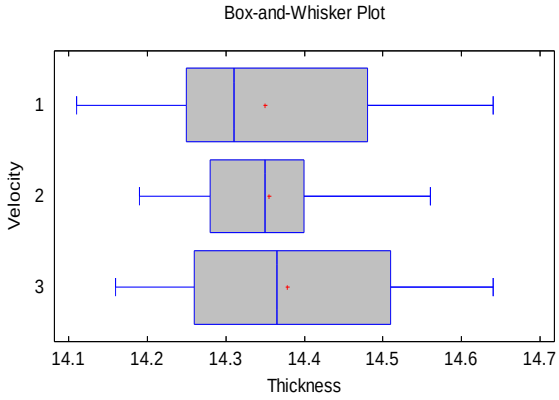

Figure 7
Tablet Thickness vs. Tablet Press Velocity

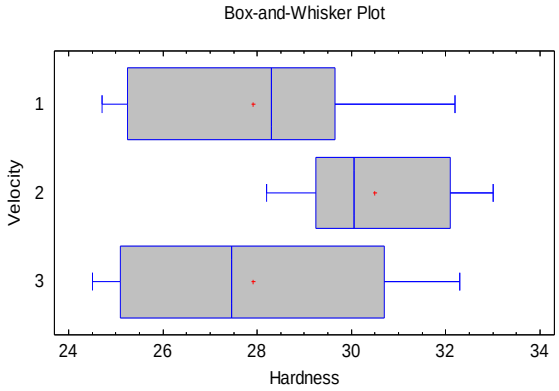

Figure 8
Tablet Hardness vs. Tablet Press Velocity

CONCLUSIONS

From the results obtained from the statistical analysis (refer to Tablet 1) it is concluded that both MLTPM process are equivalent since, the null hypothesis was accepted in each operation parameter analyzed. Also, the Kruskal Wallis test confirmed the findings in the ANOVA test.

This experiment confirmed that the ANOVA test is a useful tool to compare and analyze processes that are similar. Also, it is a tool that can complement a process validation because it has the capacity to comply with validation requirements. Moreover, can be used to develop a product in less time, when required, contributing in reducing the overall costs of development.

In this experiment no chemical testing was considered however; it is recommended to use ANOVA test also to compare the chemical test of two similar processes. This consideration will give solid evidence in establishing the equivalency of two similar processes. During the experiment unfortunately it was not allowed to take more samples for hardness. For this reason it is recommended to take more samples reading for hardness to reduce the error variation.

REFERENCES

[1] Berry I. &, Nash R. (1993). *Pharmaceutical Process Validation Second Edition* (pp.xxix). New York: Marcel Dekker, Inc.

[2] Good Manufacturing Practice (GMP), 21 Code of Federal Regulations Parts 210 and 211

[3] Lieberman H. A., Lachman L., & Schwartz J. B. (1990) *Pharmaceutical Dosage Forms: Tablets Volume 3, Second Edition* (pp. 199 - 214). York: Marcel Dekker, Inc.

[4] Montgomery D. C., & Runger G. C. (1994). *Applied Statistics and Probability for Engineers* (pp. 625-627). New York: John Wiley & Sons, Inc.

[5] Montgomery D. C. (2001). *Design and Analysis of Experiments Fifth Edition* (pp. 21, 63, 175). New York: John Wiley & Sons, Inc.