In Process Hardness Test Automation for Tablet Compression Process

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Abstract *— This article describes requirements to implement new hardness tester. The instrument was specifically for a dedicated product in the compression process area of a pharmaceutical operation. The challenge was to demonstrate reproducibility between hardness testers. The specific requirement was to identify a new way to assure the in process testing is completed as required. Actual instruments Vankel Hardness Tester was not feasible for modification in order to achieve requirements related to automation of the hardness testing to prevent human error. A project was approved for new Sotax Hardness Testers. The new instruments were required to be an automatic system with the purpose of improve reproducibility and reduce human error in test and documentation. A report must obtain only if in process testing is complete. It was also required to identify and report hardness values out of specification. Pharm grade instrument requiring stainless steel housing. Units must be Strong-Cobb (SC).*

Key Terms *– Automation, Hardness Tester, In Process Testing, Strong-Cobb (SC).*

BACKGROUND INFORMATION

In year 2007, an exception report was generated due to an incorrect in process testing sample in the compression process area for a pharmaceutical manufacturing plant dedicated to one product with twelve different dosages. The operator inadvertently tested nine (9) tablets in the Vankel Hardness Tester model VK 200. See Figure 1 below. The process required testing ten (10) tablets and obtains values to determine the pass or fail or required adjustment of the compressing machine forces. The "in process testing" is a sample classified as a destructive test to determine some characteristic of the product. In this case the in process testing was to evaluate the hardness of the tablets. Originally, the pharmaceutical company was using Vankel model VK 200 hardness classified as complete manual operation. The operator obtains the sample when a container is full of tablets. Count the required tablets for the in process testing and separate from the rest of the sample. Then test one by one in the Vankel instrument. When all tests are completed, the operator obtain the results of the tablets tested in print out. The instrument calculates the average value based on the amount of tablets tested and recorded.

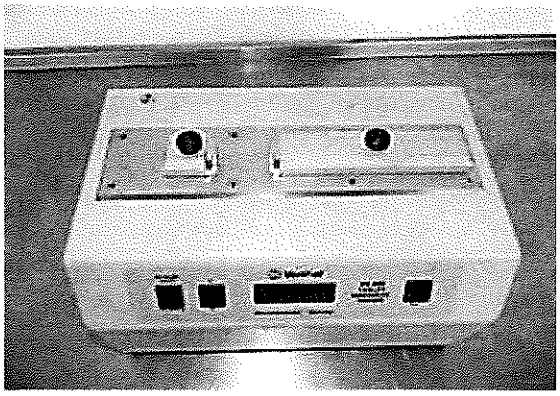

Figure 1
Vankel Hardness Tester Model VK 200

The report shows the hardness value of every tablet in Strong-Cobb (SC) units. If the operator is not alert, he can send the equipment to print out the report with less or more tablets than required for the "in process testing" and per batch record.

Even the acceptance range or specification for product is between 3 SC to 9 SC, it is prefer to maintain values between 4 SC to 6 SC. It have been demonstrated that tablets hardness values lower that 3 SC usually are soft tablets. In the other hand, if

the tablets hardness is more than 6 SC, internal fractures by excess of force occurs in the tablets. Both conditions reports broken tablet defect frequently in the compressing process. Base on this information, it is possible that an average test of nine (9) tablets can be a feasible result that may not be captured due to wide range (4 to 6 SC), neither in the quality inspection. The most common hardness testers in the pharmaceutical industries are branded as Dr. Schleuniger, Vankel, Sotax, Mitel & Erweka. In addition to the hardness test, some of these instruments include other test to be attractive. These tests are tablet thickness and tablet diameter. Also some include scales to obtain the tablet weight. Hardness is measured in different units. The measuring units of hardness for tablets follow standards for materials testing as per Cooper D, Carter S. (2009)[2]. The International System of Units (SI) is *Kilogram* (kg). The kilogram is recognized by the SI system as the primary unit of mass. *Newton* (N) is the SI unit of force; the standard for tablet hardness testing. 9.807 Newtons = 1 kilogram/ 1 Newton = 0.1020 kg. *Pound* (lb) is technically a unit of mass but can also be used for force and should be written as pound force or lbf in this case. Sometimes used for tablet strength testing in North America, but it is not an SI unit. 1 kilogram = 2.204 pounds. Historically, the tablet hardness testing evolved using units derived from specific instrument readings. *Kilopond* (kp). Not to be confused with a pound. A unit of force also called a kilogram of force. Still used today in some applications, but not recognized by the SI system. 1 kilopond = 1 kgf. *Strong-Cobb* (SC), that is our case, is a legacy of one of the first tablet hardness testing machines. Although the SC is arbitrary, it was recognized as the international standard from the 1950s to the 1980s. Strong-Cobbs are approximately 1 kg.

When we look into the history of the hardness test (based in Remington- The science and practice of pharmacy. Twenty-first Ed, Lipincott Williams and Wilkins, Philadelphia. USA; and Cooper D, Carter S. Some information on hardness testing. Engineering systems, 2009)[1][2], both concluded that started around year 80's measuring by mechanical means simply by applying force using threaded screw with spring until tablet crack. That hardness was obtained on sliding scale. The same principle was followed in Strong Cobb tester which was designed first in 1950's. But, this tester was unable to give precise readings as testing force applied by those testers that was provided by manual air pump. After this, many improved instruments were introduced where shows more precise readings and recently many electro-mechanical devices available in market with high range of sensitivity and accuracy.

Hardness test of material is indicative of its strength. On the other hand, one can say it also indicates resistance power to damage its intactness. For tablet, it reflects the internal bonding strength of granules/powder which can able to hold composite structure under applied external force. How hardness of oral formulation related to pharmacokinetics is shown by Figure 2. [1][2]

In the Remington book – (The science and practice of pharmacy.)[1], describe that the advantages of hardness test is that hardness test give an idea about the amount of force which can able to fracture as well as it will also help to access compatibility of formulation. It will also serve as guideline in handling, packaging and storage of formulation. The Disadvantages of hardness test is that it is unable to give idea about capping and lamination behavior of formulation especially in case of tablet.

The Factors affecting strength (hardness) of tablet are speed of compression, solid state structure, particle size, mechanical interlocking, solid bridges, distance forces, bonding mechanisms, volume reduction mechanisms of powder during the process of compression, surface area change during compression. [1][3][4].

Finally, it was decided to use a new instrument not only capable of reporting the exact requirements of "in process testing" but also to be automatic to facilitate the operator to do another task while the instrument is performing the test itself. The decision was to implement the Sotax

hardness tester model HT-10 particularly since this unit was identified capable of perform all requirements. However, it was necessary by the manufacturer to do some modifications in order to obtain reliable instruments. It was based on the results of preliminary engineering study. A total of four Sotax hardness instrument instruments were owned in order to get one as spare. See Figure 2 below.

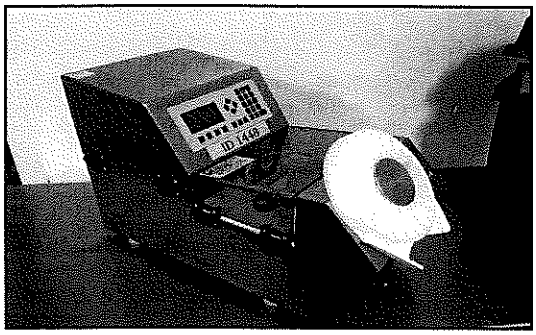

Figure 2
Pharmaceutical Sotax Hardness Tester HT-10

After the initial qualification, the instrument demonstrated consistent values considered as unreal, (Plausibility limits). The range for the tablet being test was between 3 SC to 9 SC. It was observed values as low as 1 SC consistently in all new Sotax hardness testers considered as outlier. This behavior required to put out of service the Sotax instruments and left the existing Vankel in use until identify and resolve the problem. Additional Engineering Study was conducted to confirm the reliability of the instrument being success in the implementation of these instruments after some modifications.

COMPRESSING PROCESS DESCRIPTION

The pharmaceutical plant is a dedicated facility for a product manufacturing with 12 different dosages for domestic and international markets. The manufacturing process contemplates materials weighing, mixing, and compressing process. The process is finalized with packaging process in any of the five (5) packaging lines, depending on demand. Every lot is composed of either 4, 8 up to a maximum of 10 subparts. Every subpart is granulated through a wet mix, wet mill, drying and a final blending process.

Product granulation is converted into tablets through a compressing process, using tablet press equipment. Compressing machine are complex equipment requiring to be monitored continuously to prevent malfunction. Setting of the machine by both, operator and maintenance technician is very important. There are three tablets press machines at the site. An approximately of a maximum of 700 kg of granulation (ten subparts) is transported from the manufacturing area to one of the three compressing suites. The granulation is presented to the compressing area in three plastic drums of 55 gallons. The compressing machines are model Fette 3090. The configuration of these Fette 3090 machine is that it have two sides. Each side has its own feeder and hopper. This machine has compressing roller and ejection stations per side. The only parts in common are the punches and the die table used in both sides.

The granulation is elevated over the compressing machine trough Volkmann vacuum conveyor system. The granulation fall by gravity passing through a type inverted "Y" to feed the two hoppers of the compressing machine.

The granulation then is transported to each feeder (Fill-o-Matic) to distribute the granulation in the table (Turret) evenly. See Figure 3 below.

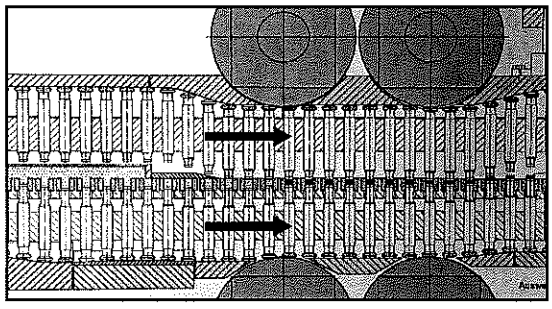

Figure 3
Compression Cycle

- **Pull Down Process:** Consists of lowering punches that are drawn into die cavities. The fill cam is the mechanism drawing punches down. Fill cam is fixed in position.

- **Overfilling Process:** It is the process where the punches are lowered to the lowest point. It also is accomplished in the filler cam. This process is to ensure there is enough granulation in the die.
- **Dosing Weight Process:** At this moment, dosing weight cam positions the punch to obtain the desired amount of granulation inside the cavity to be compressed.
- **Product Scrapper Process:** Cavities are filled with granulation product. Excess of granulation is removed with the tablet scrapper and introduced in the inside channel of the turret to pass it to the next side of the machine.
- **Pre Compressing Process:** Initial force is applied to the granulation knows as pre-compression force to remove entrapped air and eliminate capping defect in the tablet. This force is dependable of the speed of the machine and the characteristics of the granulation. Capping is a defect in the tablet where the upper layer is separated by entrapped air at the end of the compressing process.
- **Main Compressing Force:** Then after the pre compressing process, the tablet is applied to a final force know as main force to obtain the final thickness and hardness of the tablets. The ejection station is ready to divert the tablets out of the table (Turret) to the chute.
- **Tablet Ejection Process:** Upon completed the main compressing force, the tablet is removed from the die table (Turret) being diverted to the exist chute.

Then the tablets are passed through a Gratex de-duster to eliminate excess of granulation and make sure the tablets are free of metal particle by passing the product through metal detectors.

Finally the compressed product falls in the container. Every container is filled with 17 kg of product tablets with approximately 121,000 tablets per container. At the end of every filled container, ten tablets per container are test.

DESIGN PROJECT OBJECTIVES

The main objective of this project was to find an automation solution to comply with the main requirement that was to prevent hardness tester report with less or more tablets than required by the batch record and procedures. Also, be consistent with the actual measuring dimensions of Strong-Cobbs. Obtain an instrument capable of performing the test in an automatic way allowing the operators to continue with other tasks in the compression process. Assure that the instrument is pharmaceutical grade and that the reading is reliable across not only the new instrument but compared with the existing Vankel testers model VK 200.

METHODOLOGY

The new Sotax hardness test instruments and the existing Vankel instrument were challenged in one compressing area at the same time and using the same lot to maintain consistency. This way the variables are reduced for the test. It was required few operators to document the results. The idea was to simulate a lot with forty (40) containers (the maximum per lot). It was required also to evaluate that there is no outlier recorded/reported in the Sotax hardness testers. A statistical tool named Minitab was utilized to compare all population of Sotax and Vankel. Standard deviation, variability and mean test were used to compare two samples (Vankel & Sotax).

The obtained result was that both instrument brand are not significant different related to variability but, different with respect to the mean. However, the mean difference was identified that do not have impact related to the product range specification. The results were obtained after additional changes requested to the manufactured of Sotax.

DISCUSSION OF RESULTS

An initial validation for the new Sotax instruments was executed. See Figure 4 below. It was identified that the values were not similar to the existing Vankel instruments and frequent outlier

were reported in the new Sotax instrument creating a problem initially in the compressing process. It was identify that some internal parameters were necessary to be adjusted for the Sotax hardness tester in order to obtain the same values.

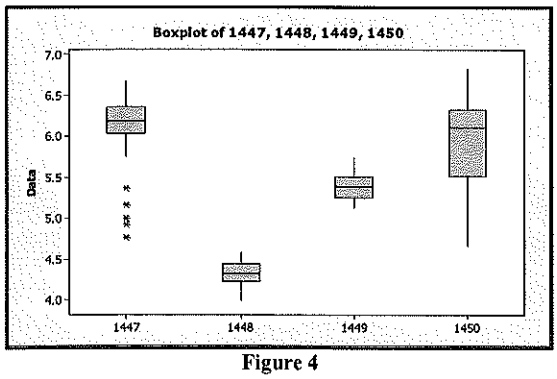

Figure 4
Box Plot

It was also identified and requested to the manufacturer some improvements required to be completed in these instruments. Brushes to clean the internal and external jaw were not large enough to clean the portion where the tablet is in contact with the jaw. New large brushes were provided and installed. It was also identified that the original jaw were made of stainless steel polished to a mirror finish in the face in contact with the tablet. A build or stick material was created after certain amount of test. This defect was generating changes in readings and sometime outlier readings. New internal and external jaws were supplied including a layer of Teflon around the jaws to prevent the product to be stick in the faces of the jaws. After the above improvements were identified a second engineering study was conducted. The instruments used for the evaluation were Sotax No. 1447, 1448, and 1449. Vankel instruments used were No. 462, 945 & 946. Of the data obtained, the minimum individual hardness value was 2.4 SCU in Vankel instrument 462. The maximum value was 5.5 SCU in Sotax instrument 1449. Even the instruments are capable of reporting minimum, maximum and average values from every sample composed of 10 tablets, the results were evaluated based in the average values only. With the tooling of Minitap tool application, the results and graphic obtained were the following to facilitate the interpretation of the data obtained. The data obtained was based to a factor P=0.05 level of confidence (95% of confidence). The following evaluation is based to standard deviation, mean and variability of the average values.

Standard Deviation

Comparing and evaluating results for Sotax Instruments Only (Inst. 1447, 1448 & 1449). Based on the data, the level of confidence is 0.052 (> 0.05). The out layers identified in the report were confirmed that are real values obtained from the print out. I can not conclude that there is a significant difference between Sotax instruments using the average values. See Figure 5 and 6 below.

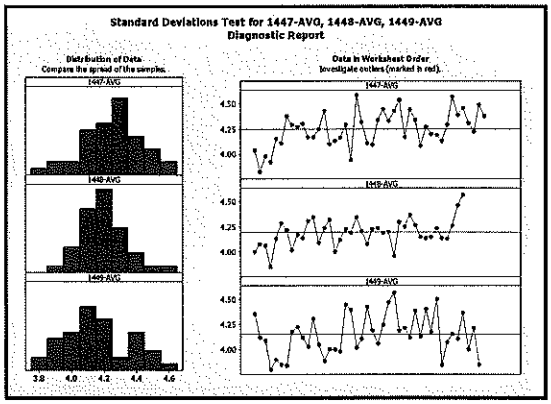

Figure 5
Sotax Diagnostic Report

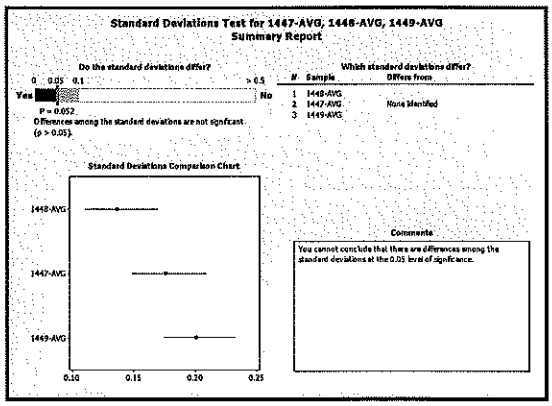

Figure 6
Sotax Summary Report

Comparing and evaluating results for Vankel Instruments Only (Inst. 945, 946 & 462). Based on the data, the level of confidence is 0.051 (> 0.05).

The out layers identified in the report were also confirmed that are real values obtained from the print out. In this case also, I can not conclude that there is a significant difference between Vankel instruments using the average values. However, instrument 946 is demonstrating an out of control graphic. Values start from low to high. Not random around the mean value. Since it is a manual operation feeding, depend greatly how the operator is handling this sample and the instrument. It could affect the reading creating that apparent out of control. See Figure 7 and 8 below.

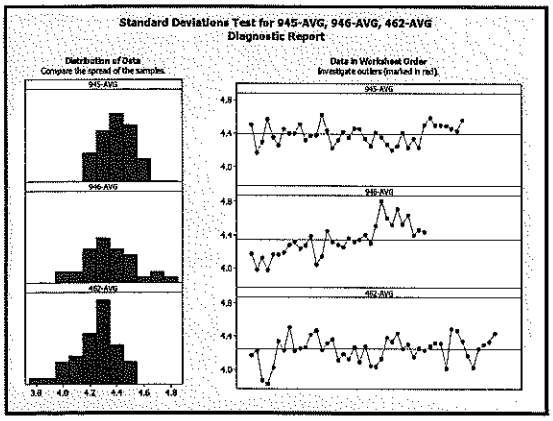

Figure 7
Vankel Diagnostic Report

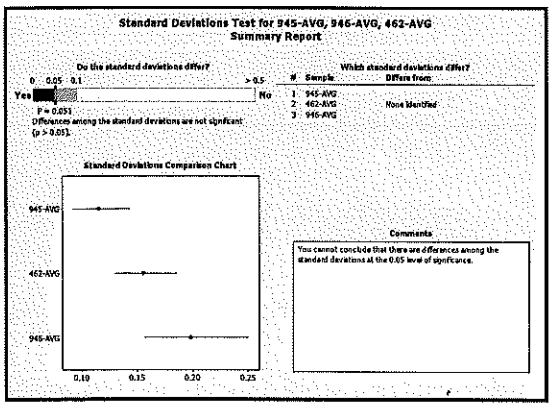

Figure 8
Vankel Summary Report

Comparing Both, Sotax and Vankel Instrument Based on the data, the level of confidence is 0.019 (> 0.05). The out layers identified in the report were also confirmed that are real values obtained from the print out. In this comparison chart, I can accept the hypothesis that there is a difference between instruments.

Below graphic is demonstrating that Vankel instruments are the most contributors in significant difference in standard deviation comparison chart. Observing the above graphics, even the Vankel instrument 945 is having the lowest deviation (approximately 0.12), the average value is the highest (4.4 SCU). For the case of Vankel instrument 946, it has the highest variation and the highest deviation of the average values. Also, this instrument is demonstrating an out of control graphically. The value points starts from low to high. Since this instrument is manual feed, it could be possible that the operator handled the sample incorrectly in the instrument by positioning incorrectly the tablet between the jaws. Another possibility could be that the moving jaw was jammed while in the process creating false out of control. See Figure 9 and 10 below.

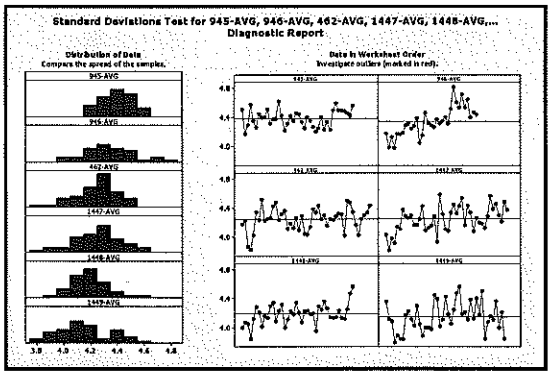

Figure 9
Sotax and Vankel Diagnostic Report

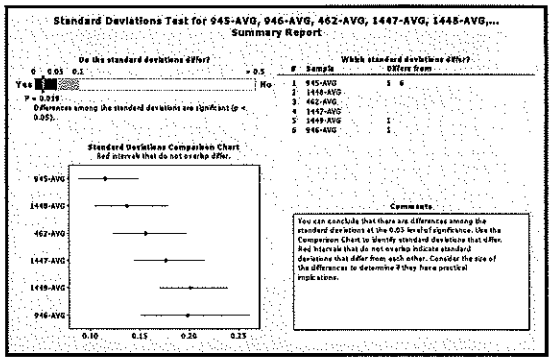

Figure 10
Sotax and Vankel Summary Report

In order to understand which of the above instrument identified as significant different (Inst 945, 946 & 1449), them were eliminated

individually from the above computations. It shows that instrument 945 is the mayor contributor to create difference between all instruments data. See the next graphics confirming the results of P factor. P= 0.105 without instrument 945, P=0.054 without instrument 1449 and P=0.015 without instrument 946.

Eliminating instrument 945 shows a P factor of P=0.105 with the remaining instruments demonstrating that there is no difference between remaining instruments. See Figure 11 and 12 below.

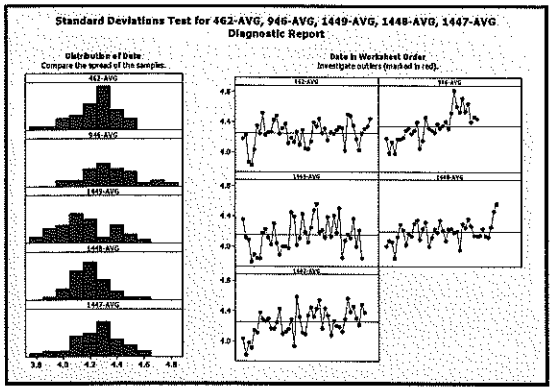

Figure 11
Diagnostic Report Eliminating Vankel 945

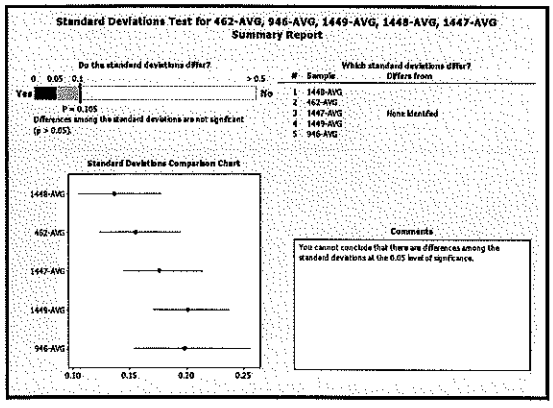

Figure 12
Summary Report Eliminating Vankel 945

Eliminating instrument 1449 shows a P factor of P=0.054 with the remaining instruments demonstrating that there is a difference between remaining instruments. See Figure 13 and 14.

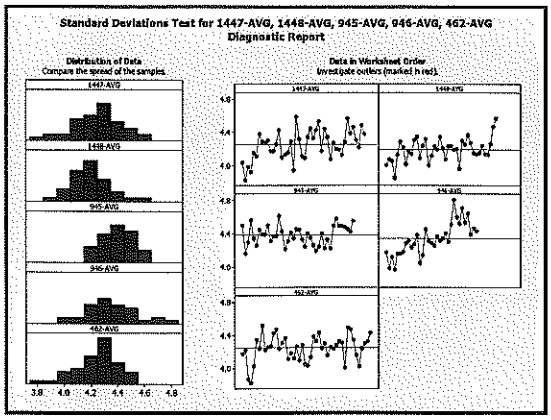

Figure 13
Diagnostic Report Eliminating Sotax 1449

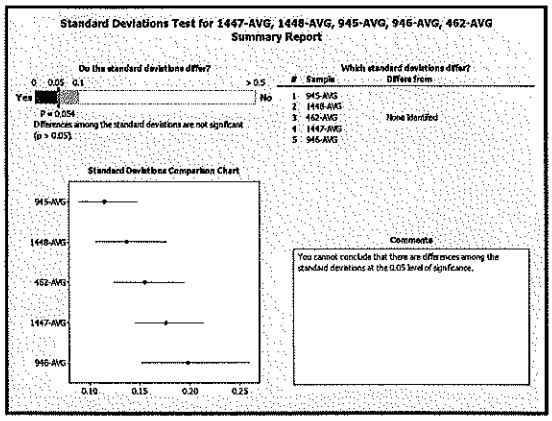

Figure 14
Summary Report Eliminating Sotax 1449

Eliminating instrument 946 shows a P factor of P=0.015 with the remaining instruments demonstrating that there is a difference between remaining instruments. See Figure 15 and 16 below.

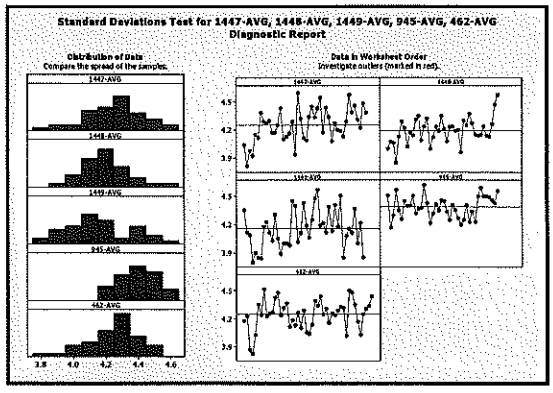

Figure 15
Diagnostic Report Eliminating Vankel 946

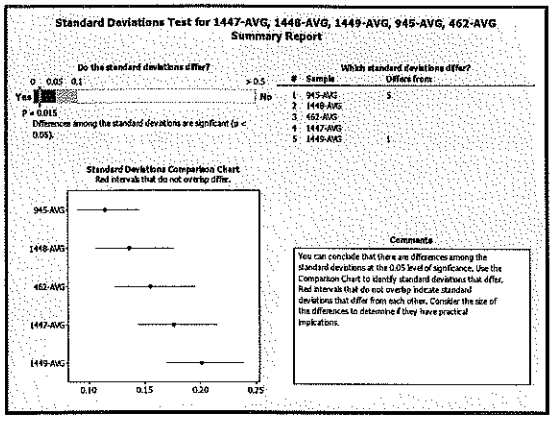

Figure 16
Summary Report Eliminating Vankel 946

ANOVA

In order to be more specific to demonstrate if there a significant difference between brands instruments Sotax and Vankel base on mean, an ANOVA calculation is performed. It concluded that both brands are different based to the P factor = 0. See Table 1 below. It is demonstrated that the Sotax instruments mean is lower (4.1987) compare with Vankel (4.3218)

Table 1
One –Way ANOVA: Sotax and Vankel

Source	DF	SS	MS	F	P
C2	1	0.9311	0.9311	31.17	0.000
Error	244	7.2876	0.0299		
Total	245	8.2187			

S = 0.1728 R-Sq = 11.33% R-Sq(adj) = 10.97%

Individual 95% CIs For Mean Based on Pooled StDev

Level	N	Mean	StDev	------+---------+---------+---------+-
Sotax	127	4.1987	0.1778	(-----*-----)
Vankel	119	4.3218	0.1674	(-----*-----)
				------+---------+---------+---------+---
				4.200 4.250 4.300 4.350

Pooled StDev = 0.1728

Process Capability & Normal Distribution

Comparing Both, Sotax and Vankel Instrument, the following charts demonstrate how it was before the change (Vankel) and how it will be after the change (Sotax) demonstrating that the normal distribution in the histogram and before/ after capability is similar. However, the change is in the mean of 0.120747 lower in the Sotax compare with the Vankel. Confirming the same behavior in the ANOVA chart. This difference is considered acceptable for the range of the process. The following Xbar-R chart confirms that the data of Vankel (Before) and Sotax (After) process condition are stable to be used for the calculations. The normally plot also is demonstrating similar results for the data used for the calculations of Vankel and Sotax instruments. See Figure 17, 18 and 19 below.

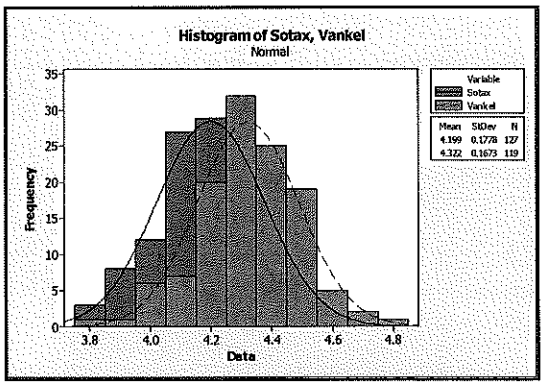

Figure 17
Histogram of Sotax and Vankel

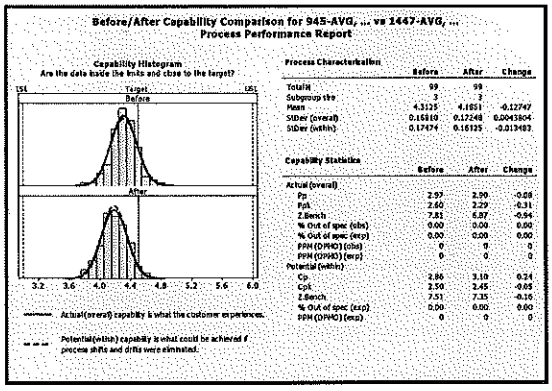

Figure 18
Process Perform Report of Sotax and Vankel

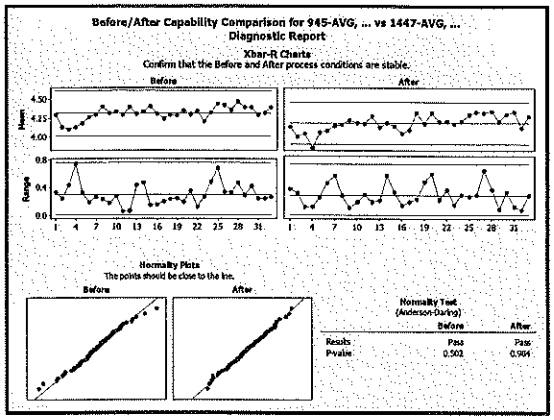

Figure 19
Xbar-R and Normally Plot Between Sotax and Vankel

Box Plot

Comparing Both, Sotax and Vankel Instrument individually, it can be observer a tendency that the new Sotax instrument (No 1447, 1448, and 1449) will maintain a mean lower than Vankel (No. 945, 946, 462). However joining the entire Sotax instrument as one set of data and Vankel in another set of data, it confirm one more time that the new instrument mean value have a tendency to report lower values than Vankel. A difference of –0.1231 in mean can be observed. See Figure 20 and 21 below.

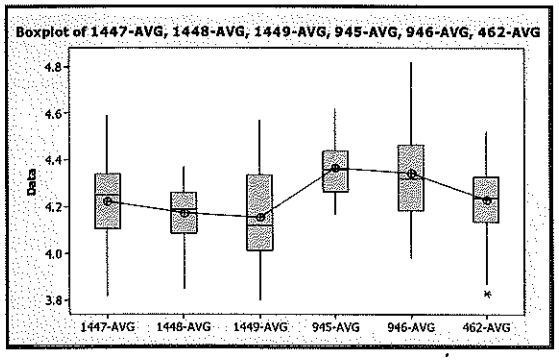

Figure 20
Box Plot Between Instruments

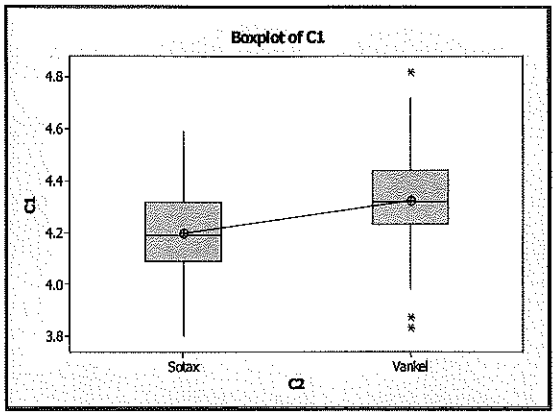

Figure 21
Box Plot Between Sotax and Vankel

2-Variances -Test & Confidence Interval

Since we have demonstrated in previous graphic that there is a significant difference in mean, I want also to evaluate the variance between instruments. See table 2 below. The following data is to demonstrate if there a significant variation in term of variance evaluating the all Sotax instruments as one set of data and Vankel instrument as another set of data. See Figure 22, 23 and 24 below.

Table 2
Test and CI for Two Variances: Sotax and Vankel

Method				
Null hypothesis Sigma(Sotax) /Sigma(Vankel) = 1				
Alternative hypothesis Sigma(Sotax) /Sigma(Vankel) not = 1				
Significance level Alpha = 0.05				
Statistics				
Variable	N	StDev	Variance	
Sotax	127	0.178	0.032	
Vankel	119	0.167	0.028	
Ratio of standard deviations = 1.062				
Ratio of variances = 1.129				
95% Confidence Intervals				
Distribution of Data	CI for StDev Ratio		F for Variance Ratio	
Normal	(0.888, 1.269)		(0.789, 1.611)	
Continuous	(0.897, 1.343)		(0.804, 1.804)	
Tests			Test	
Method	DF1	DF2	Statistic	P-Value
F Test (normal)	126	118	1.13	0.506
Levene's Test (any continuous)	1	244	0.82	0.367

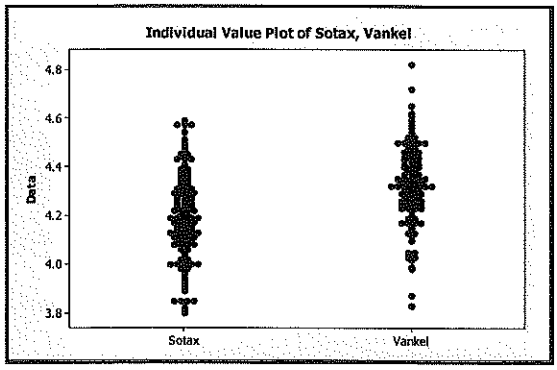

Figure 22
Individual Value Plot of Sotax and Vankel

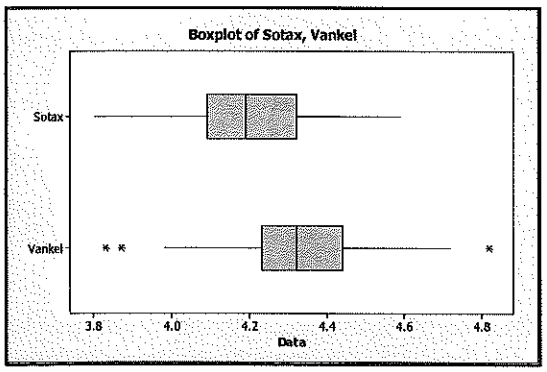

Figure 23
Boxplot of Sotax and Vankel

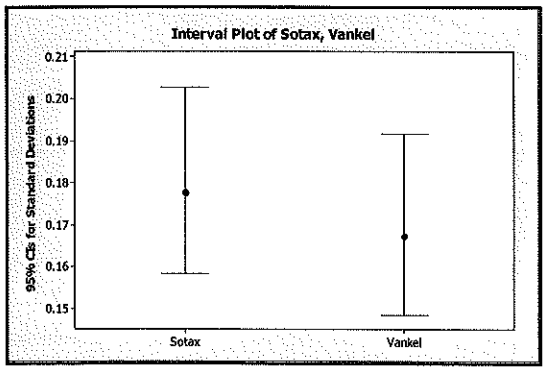

Figure 24
Interval Plot of Sotax and Vankel

CONCLUSION

From the data of average values obtained for each instrument based in a ten (10) tablets per test, it was demonstrated that every instruments brand along, there is no significant different with a confidence level of P=0.05, but comparing all instruments it can be appreciated a difference where the mean of the Sotax is lower by -0.1231 SC. However, evaluating Soatax and Vankel as different populations in terms of variances, there are no differences with a P value more than 0.01. Actual value is 0.506.

Also it showed that the instrument 946 is having the most variation and the highest deviation of average values compared with the rest of the instruments.

Observing the data overall, the delta of deviation of the average values is less than 0.1 SCU concluding that there is a difference between the equipment.

The changes applied to the Sotax instruments (new jaw with Teflon layer, sensitivity parameter in changed from 35% to 50% and larger brushes to keep the jaw cleaned) resulted in a better performance for these new equipment. Even the new instrument is reporting relatively mean values lower than actual Vankel, for the process rang of 6 to 9 SC, this difference of -0.1231is acceptable.

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