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Process Validation& Contents Uniformity in Tablets via Quality Tools and Process Capabilities

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Abstract: *This study based on such concepts and provides an overview of the quality tools such as cause & effect analysis, process capabilities and other quality tools like normality plots histograms. Box plots and other statistical techniques and a step-by-step approach for determining process capability. Which ultimately leads to overall process improvement and validation of that tablets. Which were manufactured at industrial lab. Faculty of pharmacy Hamdard university*

The above approach is illustrated in present study. As part of a process validation, A 5 mg tablet was evaluated for content and dosage uniformity. The specifications were 85-115%. Three batches were made and sampled. Thirty tablets were taken throughout the production run for each batch and thus represented the entire batch. The sample size is selected to conform to USP chapter <905>, Uniformity of dosage unit

The overall results in different interpretation were satisfactory as per normality plots histograms. Box plots and other statistical techniques .Furthermore over all process capability Cpk was found with 1.206. Which is acceptable indicator of process capability

Keywords: *Process validation, Quality tools, Statistical techniques, Content Uniformity, Process capabilities*

I. Introduction

The Food and Drug Administration has defined validation as "establishing documented evidence which provides a high degree of assurance that a specific process will consistently producing a product meeting its predetermined specifications and quality attributes. The requirement of a high degree of assurance raises the question, what is an appropriate and acceptable degree of assurance? We assert that three validation successive manufactured batches, all of whose samples meet specifications, are insufficient to provide a high degree of assurance.

A capability study measures the natural variability of a process. This variability is examined and compared to the specifications that must be met. The process is capable if the variability is consistent and small enough so that most of the dosage units produced will meet their specifications.

Kieffer[1] has maintained that the well-established statistical measures for process capability are excellent for qualifying the degree of assurance . He has further proposed that the acceptable degree of assurance should be set relative to the risk vs. benefit for the measured quality characteristic for the end user

II. Plan of work

i. Manufacturing of tablets is carried out at industrial lab. Faculty of pharmacy as per existing facility
ii. Evaluate each cause and their contributing leading to effect (content and dosage uniformity) by cause and effect diagram proposed model of cause and effect diagram expressed in Fig 1[2] , while typical process flow of process mentioned in Fig 2

Fig 1. Cause & Effect Diagram Of Tablets Validation

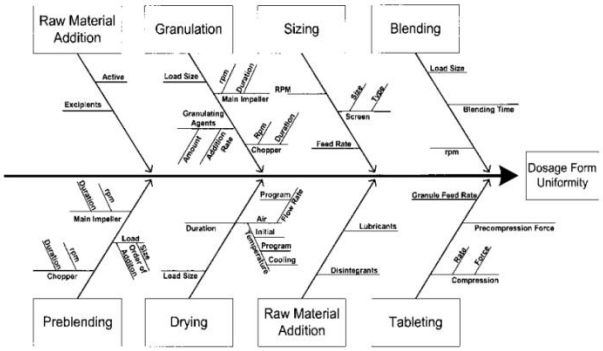
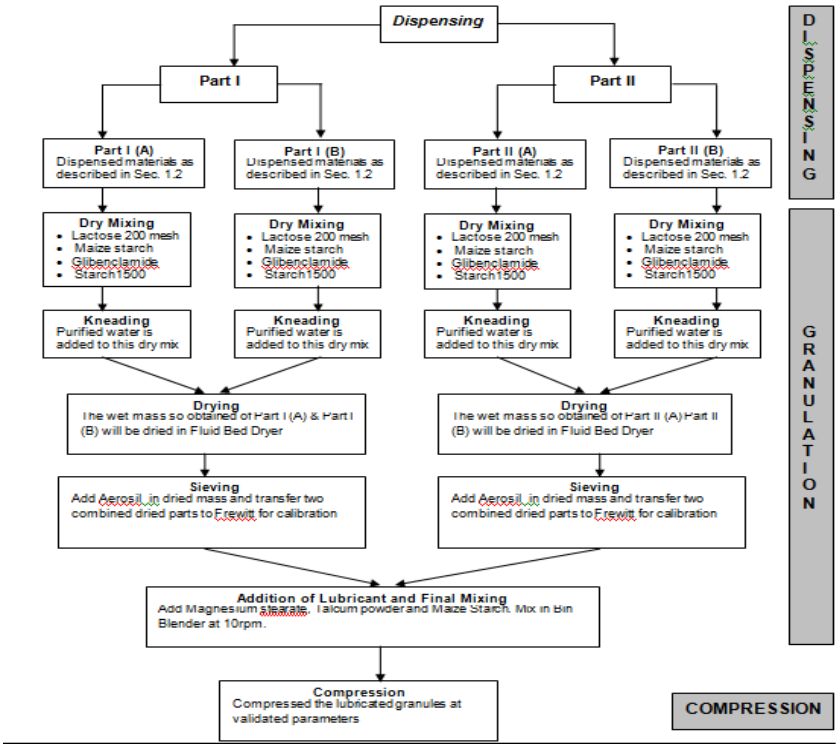


Fig. 2 PROCES FLOW TABLETS



iii. Identify critical steps during manufacturing of tablets by control charts and other quality tools in order to facilitate process validation leading to content and dosage uniformity

iv. Content uniformity of 5 mg tablets of Glibenclamide of three successive batches FI .F2 and F3 analyzed on spectrophotometer and then analyzed % content % of 30 tablets and tabulated in Table 1 .After each batch evaluated statistically A comparison is made of all of the batches .

Table 1 Content Uniformity profile of Batch F 1, F 2 and F3

TABLET	F1	F2	F3
1	100.1	99.8	96.7
2	97.6	106.3	98.5
3	94.2	100	100.1
4	99.5	99	106.9
5	100.9	102.1	102
6	105.4	104	104.1
7	104.6	103.4	104.1
8	99.2	97.7	95
9	101.3	94.7	104.7
10	100.0	99	105.2
11	100.3	103.2	107.8
12	105.9	104.3	102.6
13	109.2	109.6	105.5
14	96.9	98.1	104.1
15	99.8	95.7	101.5
16	100.1	105.6	103.4
17	106.1	95	101.7
18	99.1	101.9	100.5
19	98.2	103.2	108.3
20	96.8	104.3	112.9
21	99.7	97.6	108
22	104.8	96.1	102.9
23	102.0	104.3	102.
24	101.7	103.1	99.8
25	95.2	103.4	98.7
26	98.3	93	96.2
27	104.0	98.5	105.1
28	102.8	99.9	108.1
29	100.00	95.9	103.9
30	99.4	103.1	101.2

III. Application of Quality tools and Statistical Evaluation

The summary of the three validation batches regarding content uniformity is shown in Table 1 Note that
Data of all three batches is précised and can be explain by various statistical tools and techniques

3.1 Normality Plots

The data for batch F1,F2 and F3 first inspected visually with normality plots mentioned in Fig 3 , Fig 4 and Fig. 5 along with their statistical inferences in Table 1 , 2 and 3

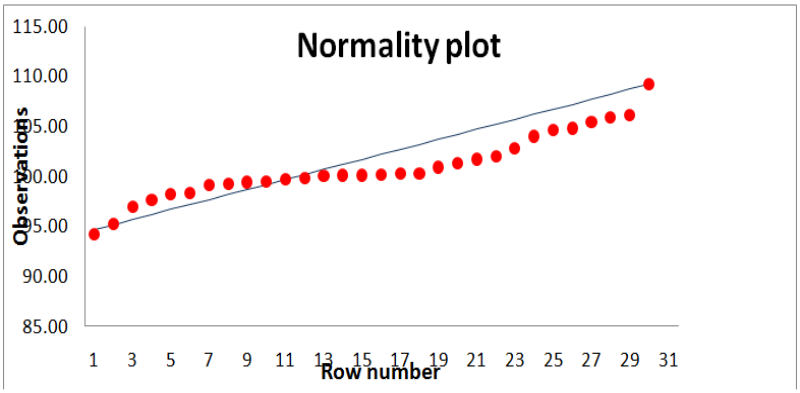


Fig 3 Normality plot of BATCH F1

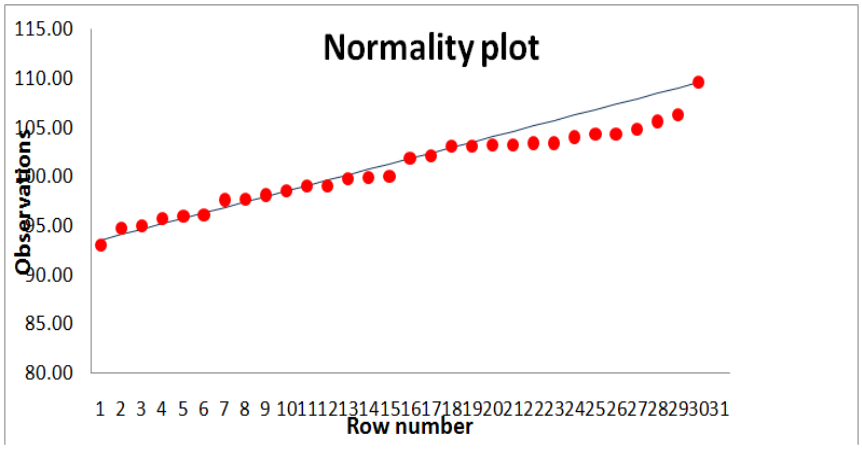


Fig 2. Normality plot of BATCH F2

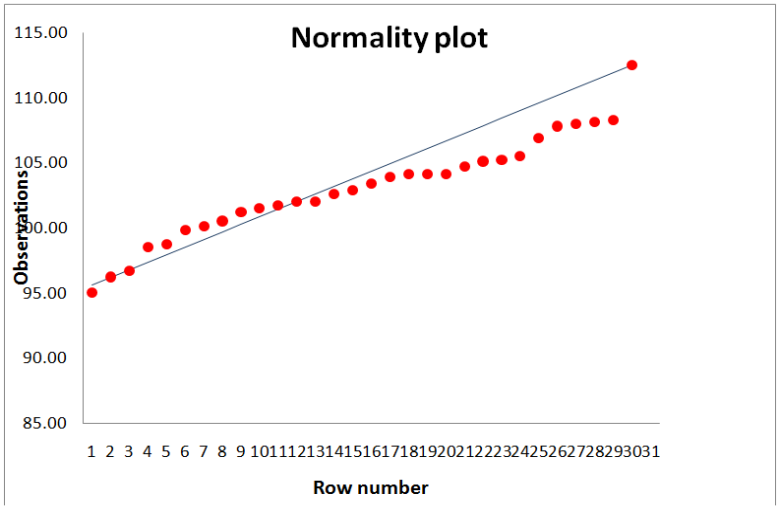


Fig 3. Normality plot of BATCH F3

Table 2. STATISTICAL INFERENCE OF BATCH F1

Results F1 Batch			Normality Table			
Statistics			Correlation normal & data	Alpha	Critical value	Conclusion
Mean (x)	100.8933333	Alpha	0.061458435	**0.01**	0.948960018	Ha
Confidence interval (x+)	102.0618815	0.05		**0.05**	0.963891667	Ha
Confidence interval (x-)	99.72478514			**0.1**	0.97066019	Ha
StDev (for sample)	3.321397019					
StDev (for population)	3.265571245					
Minimum	94.2					
Q1	99.25					
Median	100.15					
Q3	102.6	0.05				
Maximum	109.2					
Obs (n)	30					
Normality test P	-0.852433232					

P>0.05=Ho Data could be normally distributed

P<0.05=Ha Data is not normally distributed

Table 3.STATISTICAL INFERENCE OF BATCH F2

Results F2			Normality Table			
Statistics			Correlation normal & data	Alpha	Critical value	Conclusion
Mean (x)	100.7433333	Alpha	0.986906913	0.01	0.948960018	Ho
Confidence interval (x+)	102.1522275	0.05		0.05	0.963891667	Ho Accepted
Confidence interval (x-)	99.33443916			0.1	0.97066019	Ho
StDev (for sample)	4.004539091					
StDev (for population)	3.93723112					
Minimum	93					
Q1	97.8					
Median	100.95					
Q3	103.4					
Maximum	109.6					
Obs (n)	30					
Normality test P	0.073015246	0.05				

P>0.05=Ho Data could be normally distributed

P<0.05=Ha Data is not normally distributed

Table 4. STATISTICAL INFERENCE OF BATCH F3

Results F 3			Normality Table			
Statistics			Correlation normal & data	Alpha	Critical value	Conclusion
Mean (x)	103.0366667	Alpha	0.991217929	0.01	0.948960018	Ho
Confidence interval (x+)	104.4279031	0.05		0.05	0.963891667	Ho Accepted
Confidence interval (x-)	101.6454302			0.1	0.97066019	Ho
StDev (for sample)	3.954350144					
StDev (for population)	3.887885744					
Minimum	95					
Q1	100.675					
Median	103.15					
Q3	105.175					
Maximum	112.5					
Obs (n)	30					
Normality test P	0.077326262	0.05				

P>0.05=Ho Data could be normally distributed

P<0.05=Ha Data is not normally distributed

3.2 **Graphic Evaluations As per Histograms**

Graphic evaluations of all batches have computed in graphic prism pad soft ware [3]Histograms of all batches F1 , F2 and F3 are indicated in Fig 6 , 7 and 8

Fig 6 Histogram of BATCH F1

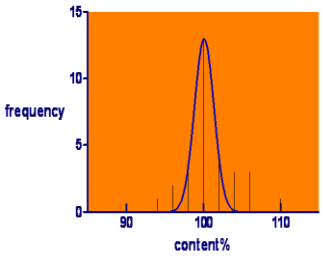


Fig 7 Histogram of BATCH F2

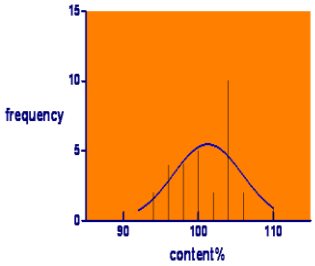
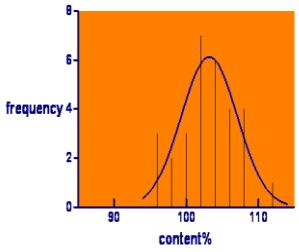


Fig 8 Histogram of BATCH F3



3.3 Box Plots

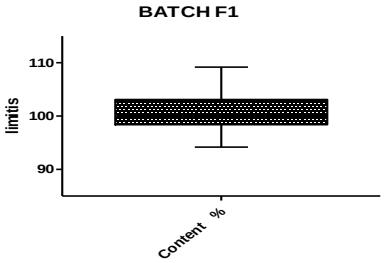


Fig. 9 Box plot of Batch F1

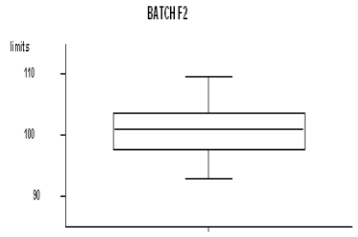


Fig. 9 Box plot of Batch F2

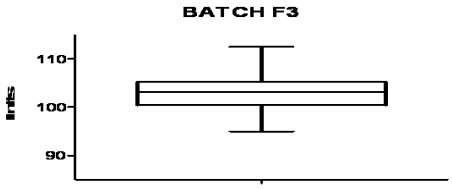


Fig11. Box plot of Batch F2

3.4 **Tolerance intervals**

Tolerance intervals parametric is another approach to find out is statement about the data values M.G Naterella[4] as well as G.Hunter[5]et all explained that tolerance interval is a statistical statement about the data value themselves.

For these data 95%/95% tolerance calculated

The procedure of computing Tolerance intervals parametric are as follows:

1. identify the continuous data
2. Find the sample size n
3. Calculate $\bar{X}$
4. Calculate Standard deviations
5. Select α , the significance (1- α)= γ =0.95
6. Select P the proportion of the population values
7. Find K = 2.549for n from Appendix 1[6]
8. Calculate $\bar{X} \pm K$s
9. We are 100 (1- α)% confidence that P% of the population values will lies between $\bar{X}$- Ks and $\bar{X}$+ Ks

3.4.1 Results of Tolerance intervals all batches

Tolerance intervals for batch F1

$\bar{X}$+ Ks = **109.2%**

$\bar{X}$- Ks = **92.3 %**

Tolerance intervals for batch F2

$\bar{X}$+ Ks = **110.8 %**

$\bar{X}$- Ks = **90.55 %**

Tolerance intervals for batch F31

$\bar{X}$+ Ks = **113.43 %**

$\bar{X}$- Ks = **93 %**

As per above estimation we can predict that all tolerances are lies between comfort zone Which have already been fulfill the criteria as set for pharmacopeial limits stated in USP [2]

mentioned in **APPENDIX II**

3.5 **C_{PK} Calculations**

The C_{pk} approach is that one would calculate single summary number that indicates the overall capability and high degree of assurance needed for the process. There are various other approaches like

Bergum's[7]method and Ruston et all and chou& Anderson [8]also emphasized and utilized these calculation with respect to probabilities and operating curve analyses

Formula for C_{pk}

Cpk = minimum (CPL, CPU)

$$CPU = \frac{(USL - \bar{X})}{3s}$$

$$CPL = \frac{(\bar{X} - LSL)}{3s}$$

Where:
USL is the upper specification limit
LSL is the lower specification limit
$\bar{X}$ is the average of the sample
s is the standard deviation of the sample

$$s = \sqrt{\frac{\sum(x_1 - x)^2}{n - 1}}$$

3.5.1 Results of all batches

C_{Pk} Result for batch F 1
C_{Pk}(min.) = 1.42
C_{Pk}(max.) = 1.58
C_{PK} Result for batch F 2
C_{Pk}(min.) = 1.19
C_{Pk}(max.) = 1.30
C_{PK} Result for batch F 3
C_{Pk}(min.) = 1.01
C_{Pk}(max.) = 1.52

IV. Result & Discussion

The data form a single group with the majority close to 100%. The values range from $\sim 94 - 110\%$.in in batch F 1

We can conclude that the data are centered near the target and lie within the specifications. To further study the shape of the data, we can compare it to the ideal shape, the normal distribution. The other two batches F2 and F3 are also confirmed with slight difference of patterns. Results of normality plots and their inferences have been reported in table 10. 11 and 12 . These profiles are provide notable results that data could be normally distributed

Histogram analysis

The data were collected throughout the production run and are representative of the process over time. To evaluate this, the 30 data values were plotted in Figure 4 as a time plot to look for any obvious trends or evidence of non randomness. This non randomness can be calculated and predicted in the Histogram analysis. The comprehensive results and Histograms of all three batches mentioned in Figure 6 , 7 and 8 as per these graphic illustration along with results. We concluded that the data didn't show an upward or downward trend or other obvious nonrandom patterns.

Box plot analysis

The batches were also compared graphically with a box plot as shown in figures 9, 10 and 11
The center line of the box plot is the median or middle value , of the data. The top of box is the 75% point and the bottom of the box is the 25% . These graphs mentioned in figures 9,10 and 11
Thus , the box plot gives a visual comparison of the center line of the data sets as well as a comparison of variability. Formal statistical tests also determined whether it is appropriate to combine the data from these batches

Tolerance intervals analysis

Results of content uniformity with respect to Tolerance intervals also very significant for example For these data, the 95%/95% tolerance interval for batch F1 is 92.3 to 109.2, which is interpreted as , "We are 95%

confident that 95% of all of the data values from these process will lie in interval 92.3 to 109.2." because the tolerance interval is smaller than the specification of 85-115%, we can be quite confident that this process will be able to meet this specification if it continues to perform in the same manner, assuming the data are approximately normally distributed The other two batches F1, F2 and F3 also have almost same statistical meaning as per above description

Process capabilities analysis

A comprehensive analyses of all three batches also proceeded with respect to process capability indices

Table 5.Summary of all batches

Batch	n	Mean	SD	C_{pk}	Tolerance interval
F1	30	100.8	3.32	1.42	92.3-109.2
F2	30	100.7	4	1.19	90.55-110.8
F3	30	103.03	3.95	1.01	93-113.43
All	90	101.5	3.75	1.206	
Specification= 85-115 %					

Table 5 is provide sufficient evidence that over all C_{pk} of all batches computed as 1.206 in contrast to individual of batch F1, F2 and F3 usually if $C_{pk}$is greater than 1.33 this value indicate that process capable and center focused. The batch F1 is fulfill the this specific requirements while other two batches going towards this value therefore , we can predict that process has tendency to achieve value as per idealized process capability assumptions. While Average $C_{pk} = 1.206$ is satisfactory agreement of overall process of three batches

Acceptable C_{pk}

Given the C_{pk} values from the three batches and the overall C_{pk}, the question now arises, what is an acceptable C_{pk}? The value of C_{pk} is related to the probability that the units of a product will be outside of the specifications. As shown in Table 5 The larger C_{pk}value, the lower the number of units, or percentage that will be of specifications assuming a normal distribution. In establishing an appropriate process capability, $C_{pk}$for a quality characteristic, one must perform a risk-benefit analysis from the user's point of view.

Acceptable C_{pk} values generally range from 1 to 2 for the quality characteristic of pharmaceuticals products $C_{pk}< 1$ are economical even for no risk

V. Conclusion

FDA's definition of validation was published in May 1987, but there has been no commonly accepted measure of the required "high degree assurance." This project has presented two statistical techniques, the tolerance interval and Cpk, as appropriate and simple measures of the degree of assurance needed for validation. The current study of tablets from an actual validation illustrates the approach. The three batches were very similar normality plots ,histogram, statistical inference , confidence intervals were combined to get an overall process capability, Cpk, of 1.206, versus the 1.33 desired. The process is going towards capability and will meet its content uniformity specification with a high degree of assurance. These recommendations also confirmed by rushton and chou[9,10] by operating curves

Along with above finding we can also be explain process validation by quality tools which give better under standing of process . This project has also great importance for pharmaceutical industry exclusively for those industry. Which are struggling to stream line their process by validation and improvements by proper application.

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