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Research Article

EVALUATION OF PROCESS CAPABILITY IN MANUFACTURE OF ANTIHYPERTENSIVE TABLETS 10 MG

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ABSTRACT

Objective: A process capability study is a formal procedure for undertaking a systematic investigation to reliably assess a process ability to consistently meet a specific requirement. Its indices are to measure the inherent variability of a process and thus to reflect its performance. This study describes the evaluation of process capability in the manufacture of antihypertensive tablets 10 mg.

Methods: This project focuses on process capability study that had been applied in the Pharmaceutical industry which includes selection of critical parameters, data collection, study on process capability, and data evaluation. In this process capability study, the critical process parameters were identified and evaluated by challenging its lower and upper release specifications. Here, many statistical process control tools along with Minitab-16 software were used to find the capability of this manufacturing process.

Results and Discussion: The discovered results for Ppk (Process performance index), tolerance limit and Standard deviation (overall) are 2.25, 40 and 2.949, which advocates that the process meets the criteria required for capability. Process capability ensures that processes are fit for industry company specification while reducing the process variation and important in achieving product quality characteristic. This capability study should be employed in the industry before the batch is made commercial. It acts as a cost-effective approach that can reduce the time taken for inspection.

Conclusion: In this research work, the current capability of the process is predicted, and the process is found to be capable.

Keywords: Process capability, Specifications, Critical parameters.

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INTRODUCTION

A plethora of process capability study in the pharmaceutical industry has been proposed recently and represented in the International Organization for Standardization/International Electro technical Commission (ISO/IEC) ISO 22514 which is a suite of standards for statistical methods in process management - capability and performance of measurement processes. This international standard was developed by an ISO software engineering working group established by the ISO and the IEC in 2012 [1-3]. A process capability study is a formal procedure for undertaking a systematic investigation to reliably assess a process ability to consistently meet a specific requirement. A process capability index defined as a quantitative way to express process variability. One-way of evaluating process capability study was conducted using Minitab-16 software [3].

Process capability analysis in pharmaceutical production

A pharmaceutical company produces products such as tablets, capsules as per customer requirements. Customer requirements are the significant features that the customers expect to find in a product. Development scientists translate those requirements into "critical-to-quality" (CTQ) characteristics of the products that they are about to produce. As example, hardness, thickness, uniformity of weight, assay, dissolution, etc., are CTQ characteristics of tablets [4]. When these CTQ characteristics are assessed and quality targets are determined, development scientists specify upper and lower limit within which variables of CTQ characteristics must fall. To evaluate production process performance, the CTQ characteristics are monitored when production in progress. A control chart is one of the tools which used to monitor the characteristics [5]. We can see whether the data of CTQ characteristics are within limit or not from control chart. Even if all the monitored data are within set limit, there is a possibility to produce a defective product. The tool by which we can say the process is capable to produce product complying customer's requirements is process capability index Cpk [6].

Hierarchy of process capability

The hierarchy of process capability is explained by Statistical process control tool where it is classified into Descriptive statistics, Process control and acceptance sampling.

The various tools are classified in Fig 1.

Simple view of process control and process capability [7-9]

Process capability can never be divorced from concepts of control charts that W.A. Shewhart envisaged. The capability of a process is independent of any specifications that may be applied to it. It is basic to the process and may be thought of as inherent process capability. This capability can be estimated from a range or standard deviation chart on past data but it can be measured only when the process itself is in control.

- Process control refers only to the "voice of the process," looking at the process using an agreed performance measure to see whether the process forms a stable distribution over time.
- Process capability measures the "goodness of a process," comparing the voice of the process with the "voice of the customer." The voice of the customer here is the specification range (tolerance) or the nearest customer specification limit.

Why is a process capability study done? [10]

1. To assess the potential capability of a process at a specific point or points in time to obtain values within a specification,
2. To predict the future potential of a process in order to create a value within specification with the use of meaning metrics, and

Table 1: Process capability versus process performance

Process capability	Process performance
Process capability requires that the standard deviation estimate come from subgroups of data (rational subgroups where variation within them is considered homogenous) This means that the variation overtime will exist between the subgroups but that the variation is homogenous within the subgroup. A control chart will be used to show the assignable cause variation that is present in the process. Cp and Cpk are the process capability indices	Process performance requires that the standard deviation estimate come from the overall data set. This means that there is no component involved in this long term estimate of the standard deviation; hence all the sources of variations are combined A histogram, stem and leaf plot, dot plot or similar graphic will show the shape of the overall data, whereas on time line there will be information on the assignable cause, variation present Pp and Ppk are the process performance indices

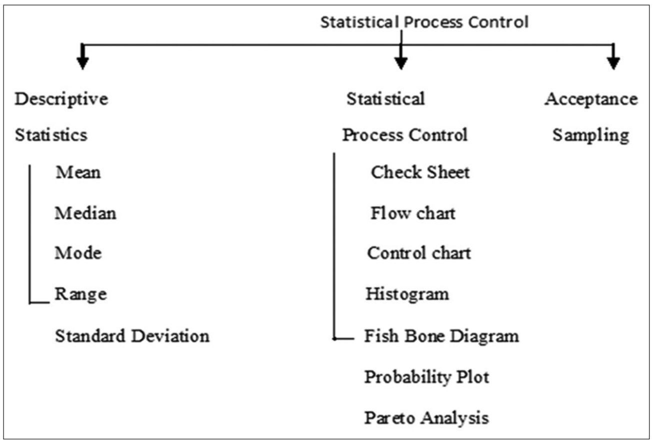

Fig. 1: Hierarchy of process capability flow chart

3. To identify improvement opportunities in the process by reducing or possibly eliminating sources of variability.

4. Process capability Vs Process Performance is explained in Table 1.

There are three conditions that must be satisfied to make process capability and performance statistics meaningful metrics:
1. The sample must be truly representative of the process. This includes the 6M's: Man, machine, material, measurements, methods, and mother nature (environmental).
2. The distribution of the quality characteristic must be Gaussian, i.e., the data can be normally distributed in a probability curve. If the data does not conform, the question is: Can it be normalized? Various analytical methods are used to potentially normalize data or apply a non-parametric analysis like box-cox transformation, Log transformation, Weibull Method, etc.
3. The process must be in statistical control. In other words, is it a stable and its variation generally random (common cause)? Note: A real-time control chart should be verifying statistical stability as process capability data is captured [11].

Do not wait until the data is taken to create a control chart, only to discover that the process trended out of statistical control along the way or had some other identifiable problem.

MATERIALS AND METHODS

Materials
Table 2 was the materials used to carry out the study.

The Equipments used during Process and source are given below in Table 3.

Equipment used during In-Process checks is given below in Table 4.

Software used in process capability study is Given below in Table 5

Table 2: Raw materials used in formulation of tablets

Ingredients	Category	Grade	Source
Anti-hypertensive drug	API	USP	Hetero drugs, Hyderabad, India
Ingredient I	Filter I	NF	FMC Bio polymers, Bangalore, India
Ingredient 2	Filter I	USP	Prayon, USA
Ingredient 3	Disintegrant	NF	Roquette, Mumbai, India
Ingredient 4	Lubricant	NF	Tyco, UK

Table 3: Equipment used during process

Name of the equipment	Source
Co-mill	Quadro, Canada
Mechanical sifter	Gansons Engineering PVT Ltd., Mumbai, India
Vaccum conveying system	PIAB, Sweden
Octagonal blender	Gansons Engineering PVT Ltd., Mumbai, India
Compression machine	ACG PAM, Mumbai, India
Metal detection unit	Techno Four Controls System, Mumbai, India
Tablet De-duster	Techno Four Controls System, Mumbai, India

Table 4: Equipment used during in-process checks

Name of the equipment	Source
Minitab	16

Table 5: Software used in process capability study

Name of the software used	Version used
Electronic weighing balance	Sartorius

Methods [12-14]
Brief description on manufacturing process of antihypertensive tablets

During all stages of the manufacturing process, temperature and humidity should be NMT 25 C and NMT 45% RH, respectively. The stages involved in the manufacturing process were as follows.

Dispensing

Raw materials used in the manufacturing were procured from the approved vendors met the specifications laid down. All raw materials should be dispensed in dispensing area of warehouse under contamination control station as mentioned in Batch manufacturing record (BMR). The dispensed raw materials were transferred to the manufacturing facility.

Milling

All the dispensed raw materials were milled using the Co-mill with speed between 1700 and 1900 RPM. Then milled materials were collected into stainless steel (SS) bins or containers. The mesh integrity and speed of mill before and after milling throughout the processing activity was checked. Finally, all the milled materials were transferred to mechanical sifter for sifting.

Sifting

The materials were sifted using mechanical sifter with appropriate sieve size. The antihypertensive drug and sodium starch glycolate were sifted using #60 and for microcrystalline cellulose, dibasic calcium phosphate (anhydrous), and magnesium stearate #40 was used. Finally, all the sifted materials were transferred to octagonal blender for the process of mixing.

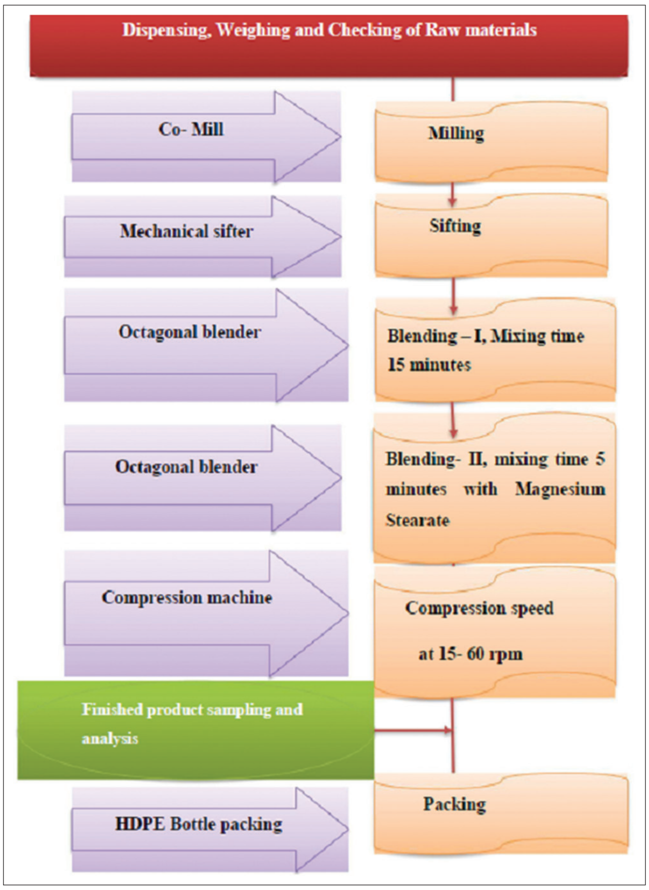

Fig. 2: Process flow chart during manufacturing process of antihypertensive tablets

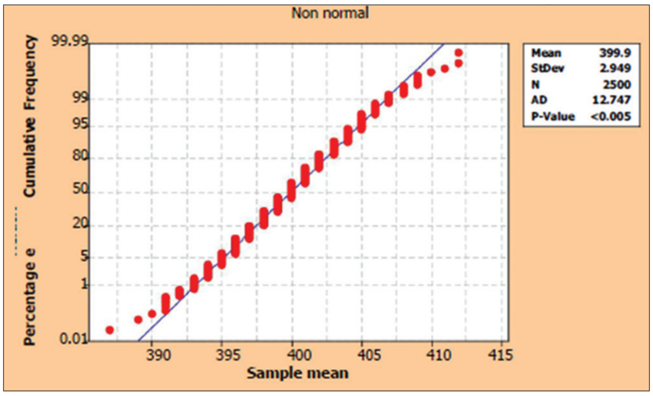

Fig. 3: Probability plot of antihypertensive tablets 10 mg

Blending

The sifted materials were loaded into the octagonal blender (900 l) using vacuum conveying system except magnesium stearate. Blender was started and run in the inch mode to check for any leakage of materials. On ensuring that there was no leakage, blending was carried out for 15 minutes at 12 RPM. Magnesium stearate was mixed with the blend taken from blender after 15 minutes of initial blending time, and blending process was performed for 5 minutes. Finally, blend was unloaded into SS bins or containers.

Compression[15]

Compression was carried out as per the BMR. Compression machine was set up with punches and dies. The machine was set and operated at different speeds of 15-60 RPM. Powder blend was loaded into hopper and compression machine was set with parameters as specified in BMR and tablets were compressed. The speed of machine and powder level in hopper before and after compression was checked throughout the process.

Packing

Compressed tablets were packed in HDPE bottles in bulk packing line. Packing was done as per the batch packing records.

Process flow chart

Process flow chart during manufacturing process of antihypertensive tablets is explained according to the Checking of raw materials,weighing and dispensing.

The probability plot of Anti-hypertensive tablets 10mg is plotted in Fig 3 below.

The Selection of control charts based on data given below in Fig 4

RESULTS AND DISCUSSION

The results of the descriptive statistics were depicted in Table 6.

1. The results for the control charts data were as follows:
   Upper specification limit = 380
   Lower specification limit = 420
   For X-bar chart:
   Centerline, X^1= 399.902
   Upper control limit, UCL X = 400.771
   Lower control limit, LCL X= 399.033
   For S chart:
   Centerline, = 2.899
   Upper control limit, UCL_S = 3.506
   Lower control limit, LCL_S = 2.273

2. The results for the normal probability plot were follows:
   AD value = 12.747
   $p<0.005$

   The results for the histogram were as follows:
   Shape of the histogram = Bell shape
   Highest frequencies were found at 401 and 400.

3. The results for the process capability indices were depicted in Table 7.
4. The results for the process performance indices were depicted in Table 8.
5. Figs. 5-8 are the summary reports of capability analysis obtained from Minitab software.

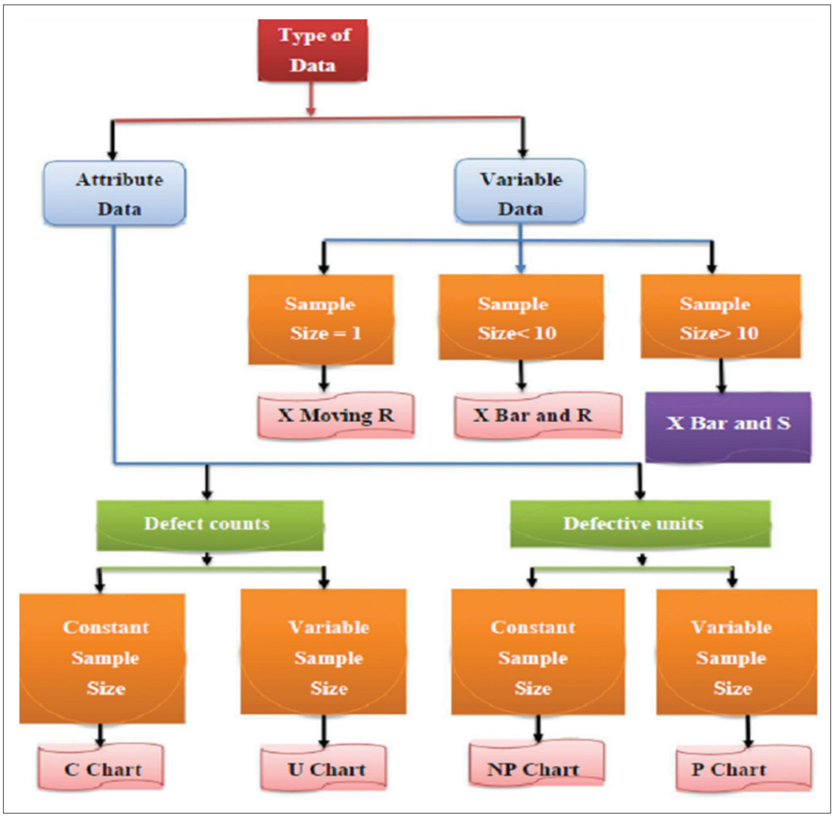

Fig. 4: Selection of control charts based on data

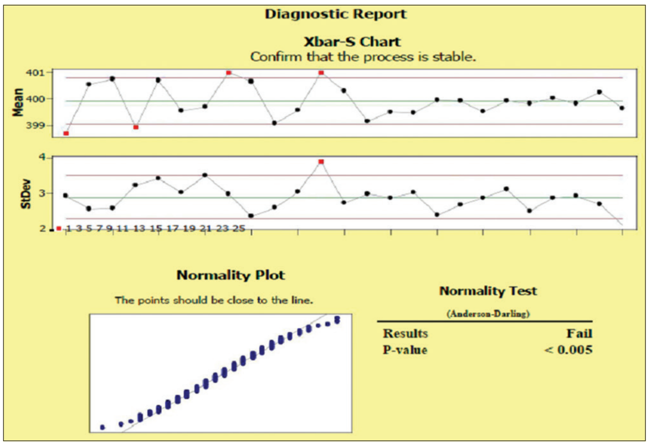

Fig. 5: Diagnostic report for capability analysis of antihypertensive tablets 10 mg

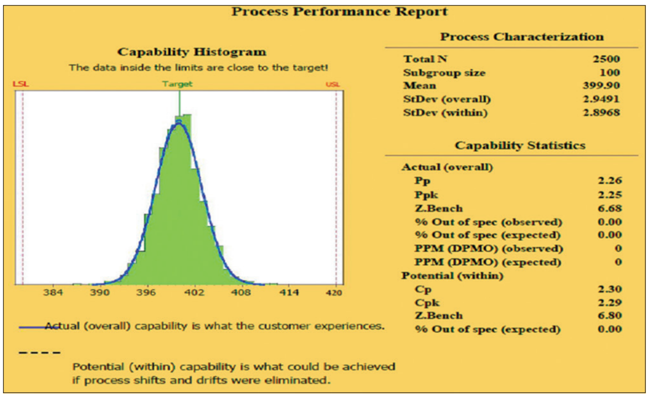

Fig. 6: Process performance report for capability analysis of antihypertensive tablets 10 mg

Table 6: Results for descriptive statistics

Descriptive statistics	Results
Process average	399.902
Standard deviation (within)	2.897
Standard deviation (overall)	2.949
Process tolerance	40

Table 7: Results for the process capability indices

Process capability indices	Results
Cp	2.3
Cpk	2.29
CpU	2.29
CpL	2.31

Table 8: Results for the process performance indices

Process performance indices	Results
Pp	2.26
Ppk	2.25
PpU	2.25
PpL	2.27

DISCUSSION

There were two critical assumptions to consider when performing process capability analyses with continuous data, namely:

1. The process in statistical control.
2. The distribution of the process considered as normal.

For statistical control process

The limits for the passing criteria as a statistical control for the points falling out of control in a process were given Table 9.

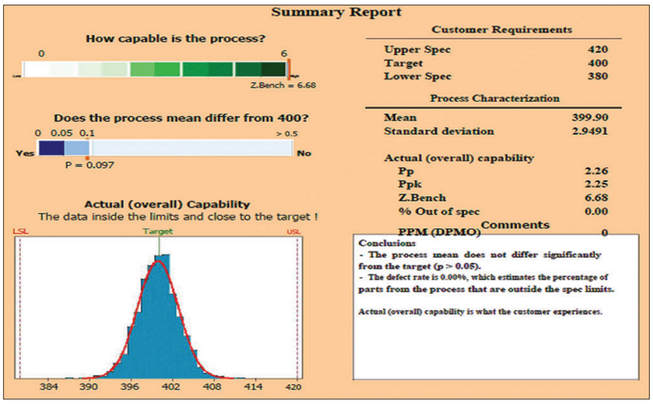

Fig. 7: Summary report for capability analysis of antihypertensive tablets 10 mg

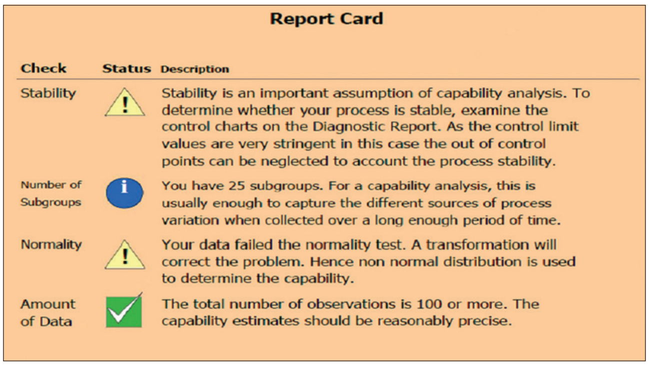

Fig. 8: Report card for capability analysis of antihypertensive tablets 10 mg

- Sample 8, mean = 401.02;
- Sample 12, mean = 401.02.

So it's concluded that the process was in statistical control as per the X-bar chart.

B. In S chart, the control limits 2 points were falling out of control out of 2500 observations. But from the above table, it indicates the process is in statistical control.

C. Distribution of the process:

From the normal probability plot graph in Fig. 2, the Anderson-Darling (AD) normality test shows that we should reject the null hypothesis, H_0: Data follow a Normal distribution vs. H_1: Data do not follow a normal distribution, at the α=0.05 significance level. This is due to the fact that the p-value for the A-D test is <0.05 and AD value = 12.747. This indicated the data was a non-normal distribution.

When the data were non-normal, we can find the process capability and process performance indices either by transforming data to a normal data through various transformation processes or directly as non-normal distribution Parameters to be considered to determine process capability based on the type of distribution were portrayed in Table 10.

A. In X-bar chart the control limits were very stringent so we can avoid the points between 398 and 402 values as mean being 400. The 4 points:
- Sample 1, mean = 398.68;
- Sample 4, mean = 398.93;

Table 9: Passing criteria limits in control charts

Passing criteria in control charts
None out of 20 observations
1 out of 30 observations
3 out of 100 observations

Table 10: Type of distribution and the parameters to be calculated

Type of distribution	Parameters to be calculated
Normal data	Process capability indices - Cp and Cpk
Non-normal data	Process performance indices - Pp and Ppk

$$\text{For a process to be capable, } Pp=\frac{(USL\text{-}LSL)}{6S}=\frac{\text{Tolerance}}{6S}=1.33$$

Implies that USL-LSL = 1.33 × 6S ≅ 8S

In non-normal for the process to be capable the following two conditions must be satisfied:

i. The standard deviation S must be <1/8th of the tolerance. In this study, standard deviation (overall) S of 2.949 and tolerance of 40 were obtained

i.e., 1/8th of the tolerance = 1/8×40 = 5

Hence, S = 2.949 < 5 we can consider it passed the first criteria and

ii. Ppk must be >1.33

Here Ppk = 2.25 which is >1.33.

Hence, we can consider that the second criterion was also passed for the test.

CONCLUSION

This study involved selection of critical quality characteristics, estimating the process capability indices of the process and interpreting the results to show that the process was under statistical control and capable. The study was conducted on a weight variation data of twenty-five batches. The overall manufacturing process was concluded as a capable process from the estimated process capability indices in the Minitab 16 software. The results of different descriptive statistics reveal that there was no significant variation between batches. From the values of the capability indices and report card of the study, we can conclude that process involved in the manufacturing of anti-hypertensive tablets 10 mg stood capable.

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