EVALUATION OF PROCESS CAPABILITY IN MANUFACTURE OF ANTIHYPERTENSIVE TABLETS 10 MG

RAHUL RAJ S, VISHAL GUPTA N*, RAVI G

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 factors 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. For 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 limits 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
To identify improvement opportunities in the process by reducing or possibly eliminating sources of variability. This means that the variation over time 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 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 over time 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 graph 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.

### Materials and Methods

**Materials**

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

The Equipment 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.

**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.

![Fig. 1: Hierarchy of process capability flow chart](image)

### Table 1: Process capability versus process performance

<table>
<thead>
<tr>
<th>Process capability</th>
<th>Process performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process capability requires that the standard deviation estimate come from subgroups of data (rational subgroups where variation within them is considered homogenous)</td>
<td>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 graph will show the shape of the overall data, whereas on time line there will be information on the assignable cause, variation present.</td>
</tr>
<tr>
<td>This means that the variation over time 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.</td>
<td>Pp and Ppk are the process performance indices.</td>
</tr>
</tbody>
</table>

### Table 2: Raw materials used in formulation of tablets

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Category</th>
<th>Grade</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-hypertensive drug</td>
<td>API</td>
<td>USP</td>
<td>Hetero drugs, Hyderabad, India</td>
</tr>
<tr>
<td>Ingredient 1</td>
<td>Filter I</td>
<td>NF</td>
<td>FMC Bio polymers, Bangalore, India</td>
</tr>
<tr>
<td>Ingredient 2</td>
<td>Filter I</td>
<td>USP</td>
<td>Prayon, USA</td>
</tr>
<tr>
<td>Ingredient 3</td>
<td>Disintegrant</td>
<td>NF</td>
<td>Roquette, Mumbai, India</td>
</tr>
<tr>
<td>Ingredient 4</td>
<td>Lubricant</td>
<td>NF</td>
<td>Tyco, UK</td>
</tr>
</tbody>
</table>

### Table 3: Equipment used during process

<table>
<thead>
<tr>
<th>Name of the equipment</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-mill</td>
<td>Quadro, Canada</td>
</tr>
<tr>
<td>Mechanical sifter</td>
<td>Gansons Engineering PVT Ltd., Mumbai, India</td>
</tr>
<tr>
<td>Vacuum conveying system</td>
<td>PIAB, Sweden</td>
</tr>
<tr>
<td>Octagonal blender</td>
<td>Gansons Engineering PVT Ltd., Mumbai, India</td>
</tr>
<tr>
<td>Compression machine</td>
<td>ACG PAM, Mumbai, India</td>
</tr>
<tr>
<td>Metal detection unit</td>
<td>Techno Four Controls System, Mumbai, India</td>
</tr>
<tr>
<td>Tablet De-duster</td>
<td>Techno Four Controls System, Mumbai, India</td>
</tr>
</tbody>
</table>

### Table 4: Equipment used during in-process checks

<table>
<thead>
<tr>
<th>Name of the equipment</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minitab</td>
<td>16</td>
</tr>
</tbody>
</table>

### Table 5: Software used in process capability study

<table>
<thead>
<tr>
<th>Name of the software used</th>
<th>Version used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic weighing balance</td>
<td>Sartorius</td>
</tr>
</tbody>
</table>

### 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.

**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**
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 10 mg is plotted in Fig 3 below.

**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, \( \bar{X} \) = 399.902
     - Upper control limit, UCL, \( X \) = 400.771
     - Lower control limit, LCL, \( X \) = 399.033
   - For S chart:
     - Centerline, \( \sigma \) = 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.
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.

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

Table 6: Results for descriptive statistics

<table>
<thead>
<tr>
<th>Descriptive statistics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process average</td>
<td>399.902</td>
</tr>
<tr>
<td>Standard deviation (within)</td>
<td>2.897</td>
</tr>
<tr>
<td>Standard deviation (overall)</td>
<td>2.949</td>
</tr>
<tr>
<td>Process tolerance</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 7: Results for the process capability indices

<table>
<thead>
<tr>
<th>Process capability indices</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_p$</td>
<td>2.3</td>
</tr>
<tr>
<td>$C_{pk}$</td>
<td>2.29</td>
</tr>
<tr>
<td>$C_{pU}$</td>
<td>2.29</td>
</tr>
<tr>
<td>$C_{pL}$</td>
<td>2.31</td>
</tr>
</tbody>
</table>

Table 8: Results for the process performance indices

<table>
<thead>
<tr>
<th>Process performance indices</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_p$</td>
<td>2.26</td>
</tr>
<tr>
<td>$P_{pk}$</td>
<td>2.25</td>
</tr>
<tr>
<td>$P_{pU}$</td>
<td>2.25</td>
</tr>
<tr>
<td>$P_{pL}$</td>
<td>2.27</td>
</tr>
</tbody>
</table>

**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 in Table 9.
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, H₀: Data follow a normal distribution vs. H₁: 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:

1. Sample 8, mean = 401.02;
2. 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.

So for a process to be capable, Pp = \( \frac{USL-LSL}{6S} \) must be greater than 1.33.

C. Normality of the data:

The Anderson-Darling test is a statistical test of whether or not a sample of data comes from a normal distribution. It is a general test of normality, which means that it can be used to test the normality of any distribution, not just the normal distribution. It is generally considered to be more powerful than the Shapiro-Wilk test for small sample sizes.