Research Article

Statistical Process Control as a Tool to Control Weight Uniformity of Tablets

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ABSTRACT

Quality of a product can be controlled at two distinct phases of manufacturing process: Post-process control and In-process control. Post process control is a postmortem study and leaves no scope for improvement as the entire batch has been produced; whereas in-process control provides surveillance and feedback for keeping processes in control and hence provides scope for improvement. Aim of the present work was to apply statistical control tool such as control charts and frequency distribution curve to weight variation of tablets which is the main In Process Quality Control (IPQC) variable affecting the dosage variation. Limitations of Pharmacopoeial specifications for weight variation test and current practice in industries which needs reference have been highlighted. Cipium tablets were prepared by wet granulation method. The tablets were collected from both the sides of double rotary compression machine in small groups in the order of compression and weighed individually at every half an hour. Pharmacopoeial compliance for weight variation was checked and Mean, Range and SD charts were plotted which were used to check the state of the process. Inspection of the control charts indicated that some disruption of uniformity occurred during the compression but Pharmacopoeial compliance was observed.

Keywords: Statistical Process Control (SPC), Control charts, Frequency Distribution Curve (FDC)

1. INTRODUCTION

Statistical Process Control (SPC) is a branch of statistics that combines rigorous time series analysis methods with graphical presentation of data, often yielding insights into the data more quickly and in a way more understandable to lay decision makers [1]. The basic theory of statistical process control was developed in the late 1920s by Dr Walter Shewhart, a statistician at the AT&T Bell Laboratories in the USA, and was popularized worldwide by Dr W Edwards Deming. As per that theory, processes that exhibit special cause variation are unstable and unpredictable, they should be improved by first eliminating the special causes in order to bring the process ''into control''. In contrast, processes that exhibit only common cause variation will continue to produce the same results, within statistical limits, unless the process is fundamentally changed or redesigned [2].

Control chart is a tool for SPC which is a graphical representation of certain descriptive statistics for specific quantitative measurements of the manufacturing process [3].

It can distinguish common and special cause variation [4]. The four main reasons for using a control chart includes: to monitor a process in

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order to determine if the process is said to be in statistical control or not, to estimate the parameters of a process, to reduce the variability of process if the process is out of control, and to identify the amount and nature of variation in the process over time. Three basic elements of Control Charts includes central line (CL), Upper control limit (UCL) and Lower control limit (LCL) [5-7].

There are two obvious sources of variability affecting the drug dosage in tablets-namely, the variation in weight and the variation in per cent composition [8]. Tablet dimensions, weight, hardness, friability, disintegration, and dissolution are some of the important quality attributes to ensure suitability of the tablet for intended use [5]. *Hashmat D et al* plotted Shewhart quality control charts for weight variation, tablet hardness and thickness of optimized formulation [9]. Tablet weight is the most important IPQC parameter to be controlled in the manufacturing process. It is not reasonable to expect that each tablet should have an identical weight, precisely equal to some target value. A tablet machine is simply not capable of producing identical tablets. The variability is due, in part, to (a) the variation of compression force, (b) variation in filling the die, and (c) variation in granulation characteristics. In addition, the balance used to weigh the tablets cannot be expected to give exactly reproducible weighing, even if the tablets could be identically manufactured. Thus the weight of any single tablet will be subject to the vagaries of chance from the foregoing uncontrollable sources of error, in addition to other identifiable sources which we have not mentioned. To achieve this objective, we decided to plot mean and variability chart for weight variation of tablets [7].

There are some methods for constructing multivariate control charts in the literature. However, these methods are usually restricted to the case of normal distributions and are difficult to visualize and interpret. The main idea behind our control chart is to reduce each multivariate measurement to a univariate. Most manufacturers use versions of the early control charts which track sample mean (X-bar charts) and sample range (R charts) or standard deviation as checks on the process state and the process variability [10-12].

Pharmaceutical industry and machinery has evolved over a period of time but the Pharmacopoeial specifications still stand as they were. This project is an attempt to highlight those areas of Pharmacopoeial specifications and current practice in industry which need reference and also to implement statistical parameters like Statistical Process Control Charts and Frequency Distribution Curve to achieve optimum product quality.

1.1. Limitations of Pharmacopoeial weight variation test

Pharmacopoeia specifies a sample size of 20: Tablet compression machines have improved over a period of time. In earlier days there were single stroke machines which have improved to single rotary and double rotary compression machines with 27, 35 and more number of stations. Taking samples of 20 with such tablet machines in production is not a practical approach as it would not be possible to have samples tested from each set of die and punches.

Limit has been specified with respect to Mean and not Target: For example, for a tablet with a target weight of 100 mg, the 10% allowable range is 90-110 mg with respect to target. If 20 tablets collected during the compression process had mean weight of 93 mg, the 10% allowable range with respect to mean would be 83.7-102.3 mg. Consider a tablet weighing 84 mg. Although this tablet would be differ 16 mg from the target, it would pass as per mean limits.

There is no consideration for standard deviation: Normal Distribution Curve is defined by two parameters i.e. Mean and Standard Deviation. Standard deviation determines the deviation of the population from the Mean. Since there is no consideration for SD, population spread cannot be obtained [13-15].

Table 1 Limits calculation for control charts

	Cipium 20 LHS	Cipium 20 RHS	Cipium 35 LHS	Cipium 35 RHS
For mean chart				
Target value	120 mg	120 mg	120 mg	120 mg
A_2	0.18	0.18	0.095	0.095
UCL	121.32 mg	121.44 mg	120.92 mg	120.98
LCL	118.68 mg	118.56 mg	119.08 mg	119.02
CL	120 mg	120 mg	120 mg	120 mg
UCL (in terms of weight of 20 tablets)	2.426 g	2.428 g	4.232 g	4.234 g
LCL (in terms of weight of 20 tablets)	2.373 g	2.371g	4.167 g	4.165 g
CL (in terms of weight of 20 tablets)	2.400 g	2.400 g	4.200 g	4.200 g
For Range chart				
D_3	0.414	0.414	0.553	0.553
D_4	1.585	1.585	1.448	1.448
UCL	11.62	12.68	13.99	14.96
LCL	3.04	3.31	5.35	5.72
CL	7.33	8.00	9.67	10.33
For SD chart				
B_3	0.51	0.51	0.679	0.679
B_4	1.49	1.49	1.330	1.330
UCL	3.27	3.79	3.32	2.88
LCL	1.12	1.30	1.69	1.47
CL	2.20	2.55	2.49	2.16

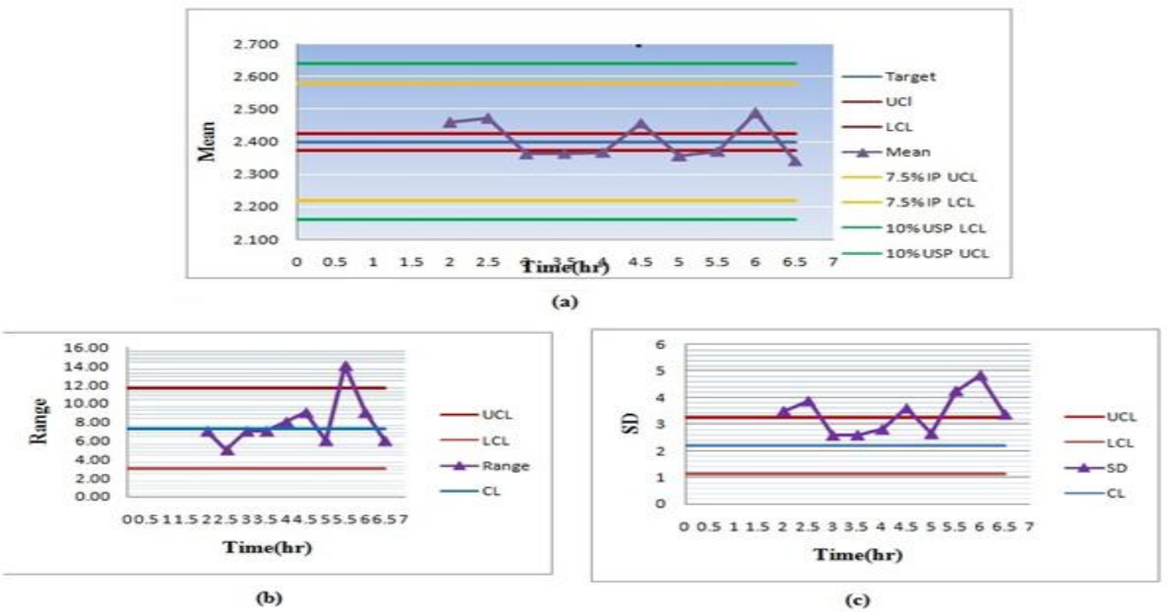

Figure 1 (a) Mean chart, (b) Range chart and (c) SD chart of Cipium 20 LHS

2. EXPERIMENTAL WORK

2.1. Tablet Preparations

Cipium (Chlorpheniramine maleate, 4 mg) tablets were prepared having target weight of the tablet as 120 mg. The drug constituted approx. 3.33% of the tablet weight. The tablet blend was prepared according to standard manufacturing procedure. The tablets were compressed using GMP certified double rotary compression machine (Model no: CJB 3) having 35 stations which was operated at a speed of 22 rpm. The batch size was 25 lakh tablets. Hoppers were filled; the machine was adjusted for correct weight and pressure, and allowed to run for about 0.5 hour.

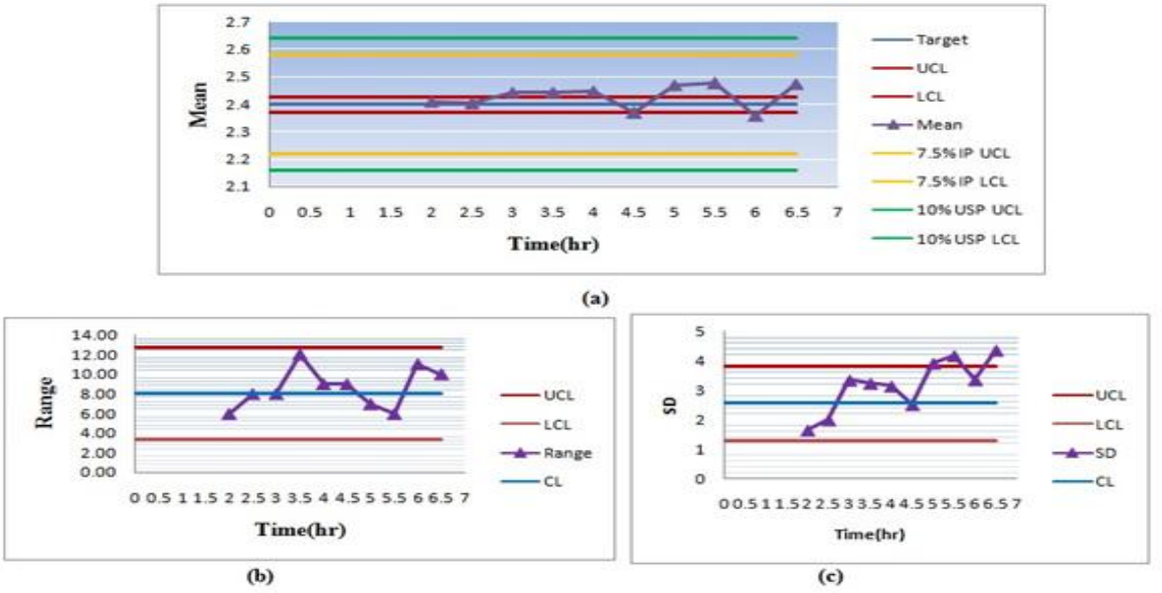

Figure 2 (a) Mean Chart, (b) Range chart and (c) SD chart for Cipium 20 RHS

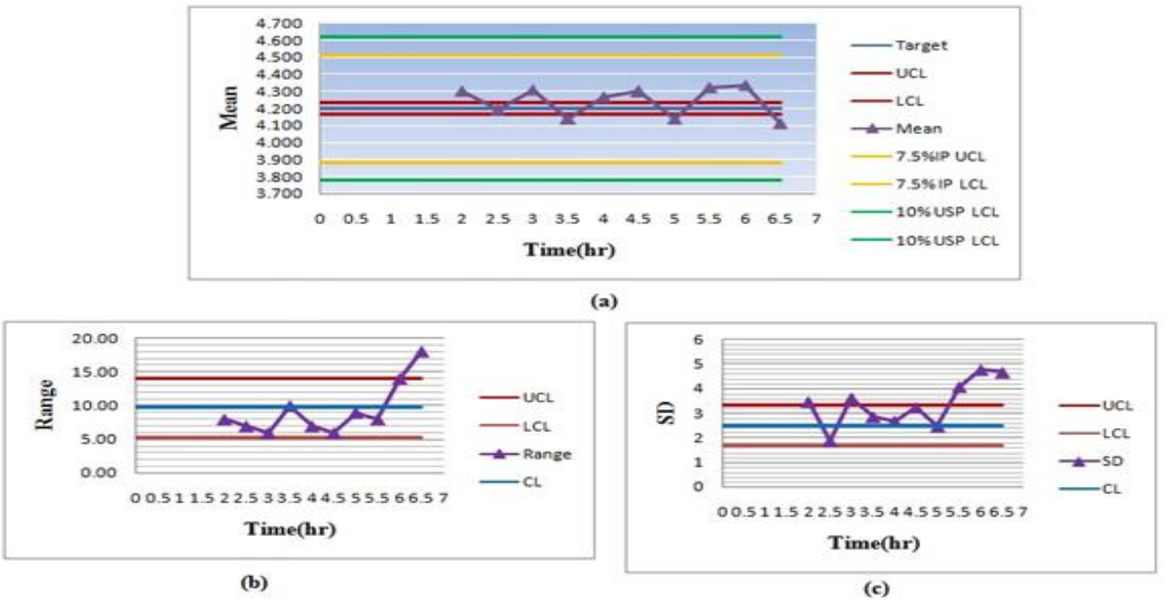

Figure 3 (a) Mean Chart, (b) Range chart and (c) SD chart for Cipium 35 LHS

2.2. Sample Collection

2.2.1. Rationale subgroup

The question of how many tablets to choose at each sampling time (rational subgroups) and how often to sample is largely dependent on the nature of the process and the level of precision required. The larger the sample and the more frequent the sampling, the greater the precision, but also the greater will be the cost.

If possible, the subgroup sample size should be constant. Otherwise, the construction and interpretation of the control chart is more difficult. In the present research, two studies were conducted simultaneously.

In one subgroup sample size was 20 to comply with Pharmacopoeial specification and in other sample size was 35 as per number of stations of compression machine.

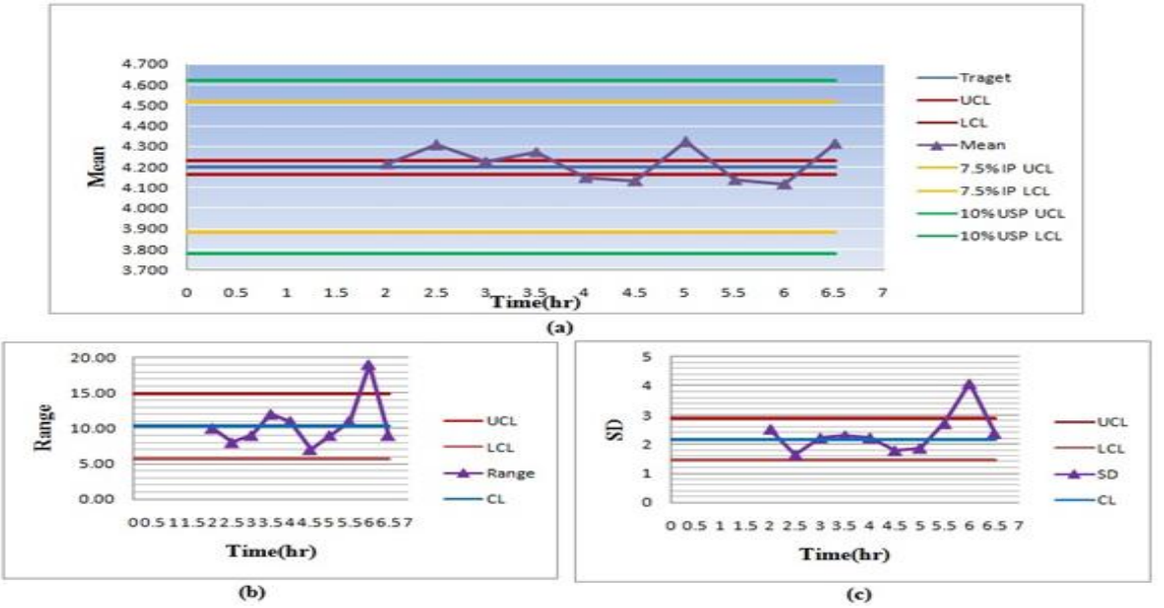

Figure 4 (a) Mean Chart, (b) Range chart and (c) SD chart for Cipium 35 RHS

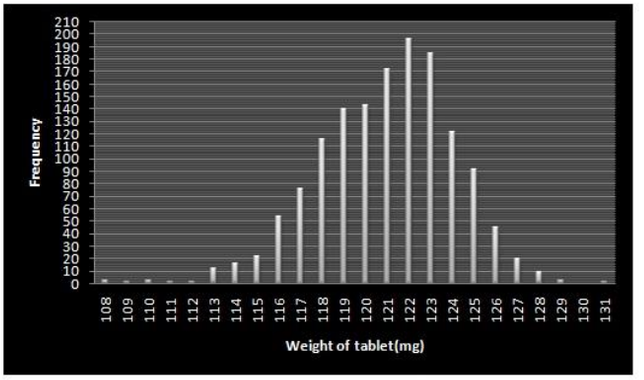

Figure 5 Frequency distribution curve of Cipium tablets

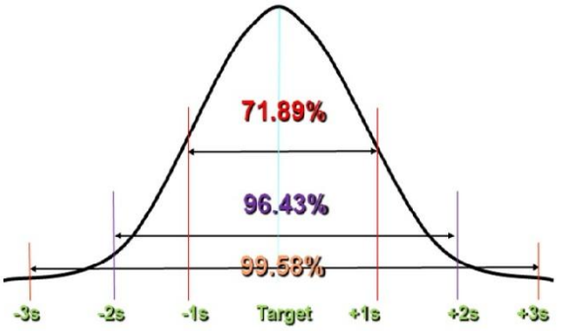

Figure 6 Population spread of Cipium Tablets

Checking the weight of tablets is a simple and non destructive test hence larger sample size doesn't affect the cost of the process.

2.2.2. Sampling plan:

2.2.2.1. Sample number as per Pharmacopoeial specifications

20 samples were collected at 0.5 hr, 1 hr and 2 hr from both sides (Left hand side and Right hand sides) of double rotary compression machine. The tablet weights were first checked for compliance of Pharmacopoeial weight variation test.

Mean, range and SD of all 20 tablets at 0.5 hr, 1 hr and 1.5 hr were calculated using equations 1, 2 and 3 respectively.

Mean =Total weight of all tablets/ N **(Equation 1)**

Where, n= number of samples

Range = Xmax - Xmin, **(Equation 2)**

Where, Xmax: Maximum observation and

Xmin : minimum observation

$$SD = \sqrt{\frac{\sum(X-\mu)^2}{N}} \quad \textbf{(Equation 3)}$$

Where, SD = Standard Deviation

X = Observation

μ = Mean

N = no. of observations

Average of mean, range and standard deviation of first three sampling points (0.5 hr, 1 hr and 1.5 hr)

were determined and symbolized as $X_{i=1\ to3}$, $R_{i=1\ to3}$ and $S_{i=1\ to3}$. These values were used to plot control charts using statistical calculation mentioned below.

2.2.2.2. Sample size as per number of stations of the tablet press

Same procedure was followed as mentioned above except the no. of samples collected at specified interval was 35 instead of 20.

2.2.3. Establishment of Control limits

To construct central line for mean chart, target value (120 mg) was considered rather than mean value of pooled samples. The *action* lines were constructed to represent 3 σ from the target value. These 3 sigma limits were constructed using following statistical equation:

For Mean chart:

Upper Control limit (UCL) = $T + A_2 \bar{R}$

Lower Control Limit (LCL) = $T - A_2 \bar{R}$

Central line (CL) = Target weight = 120 mg for Cipium tablet

For Range chart:

UCL = $D_4 \bar{R}$ and LCL= $D_3 \bar{R}$, CL= $\bar{R}$

For SD chart:

UCL =$B_4 \bar{S}$, LCL= $B_3 \bar{S}$, CL= $\bar{S}$

Where,

T = Target weight = 120 mg for Cipium tablets

$\bar{R}$ = Average range of first three sample points = $(R_1+R_2+R_3)/3$

$\bar{S}$ = Average SD of first three sample points= $(S_1+S_2+S_3)/3$

After establishment of control limits in chart, 20 samples were collected at regular intervals of 0.5 hrs after 2 hour till the end of the process. In the present study, total weight of tablets was plotted instead of mean in mean chart for convenience of an operator. Constant values for calculation for limits of control charts depend on sample size. For example, a) for sample size of 20; A_2, D_3, D_4, B_3 and B_4 was 0.180, 0.415, 1.585, 0.510 and 1.490, respectively and b) for sample size of 35; A_2, D_3, D_4, B_3 and B_4 was 0.095, 0.553, 1.448, 0.679 and 1.330, respectively. IP and USP specifications with respect to target were also plotted in each mean chart. Total weight, range and SD of these composite of 20 samples were plotted in mean, range and SD chart, respectively.

2.3. Frequency Distribution Curve (FDC)

FDC and Population spread between Target ± 1σ, Target± 2σ and Target ± 3σ were plotted using the individual weights of all pooled tablets. Yield of the process was also determined.

3. RESULTS AND DISCUSSION

3.1. Interpretation of control charts

The identification of control chart patterns is very important in statistical process control. The process is considered to be under control as long as mean, range and SD chart of the subgroup samples fall within the lower and upper limits.

Cipium tablets collected as per Pharmacopoeial specification: Calculated control limits of mean, range and SD chart are reported in table 1. As per mean charts, all or majority of the sampling points were beyond the control limits,which indicated that process was not in a state of control . Any observations outside the limits signaling the presence of a special cause requires immediate investigation [16]. The variability in the tablet manufacturing is due to variation in compression force, variation in die filling and variation in granular characetristics. In addition , the balance used to weigh the tablets cant expected to give exactly reproducible weights, even if the tablets could be identically manufactured. The reason for this special cause of variation should be found and eliminated from the manufacturing process. In Cipium 20 LHS, range chart indicated that variability of the process was quite stable except the range of samples at 5.5 hour which shows out of control point. Whenever a single point falls outside the 3 sigma control limits, a lack of control was indicated. The probability of this happening is rather small, it is very likely not due to chance. In case of range chart, majority of the points were within the limits because of wider control limits. This is because of larger deviation of individual values from the Target value in case of first 3 sampling points. If the limits are set too wide there

is a high risk of a ‘‘type II error’’ analogous to a false negative results. In range chart of Cipium 20 LHS, 4 out of 5 successive values fall on the same side of the centerline indicated lack of control. Six and three points were falling outside SD chart of Cipium 20 LHS and Cipium 20 RHS control limits, respectively indicating that process failed in SD chart (Figures 1 and 2). Range and SD both indicated variability of the process but there was a difference in results of both. SD produced aacurate results hence it covered individual weight of all the tablets and SD was calculated with respect to Target and not Mean.

*Cipium tablets collected as per number of station of compression machine:*Individual weight of seven tablets were complied USP specifications but failed to comply IP/BP specifications, which indicated IP is more stringent than USP in weight variation test for target weight of 120 mg. Six tablets had weight outside USP limits in Cipium 30 LHS and RHS. In Cipium 20 LHS and RHS, not a single tablet was outside the limit indicated that it may miss the original situation. Many times weight variation problem may be due to any one punch malfunction in compression machine. So it is necessary to collect samples based on number of station so we can get at least one sample from each station. Calculated control limits of mean, range and SD chart are reported in table 1. In Cipium 35 LHS and 35 RHS, points are falling outside the limits of mean, range and SD chart hence it also indicated that process was not in the state of control and corrective actions were necessary (Figure 3 and 4). During investigation of failure, one should appreciate that a process can change in such a way that (a) only the average is affected; (b) only the variability is affected, or (c) both the average and variability are affected. A change in average weight may be caused by maladjustment of the tablet press. Increased variability may be due to some malfunction of one or more punches. A combination of lower weight and increased variability probably would be quickly detected if half of the punches were sticking in a random manner. So all the points should fall within limits of both, mean and variability chart, for statistical process control.

3.2. Frequency Distribution Curve

It indicated that 71.89% of the population lied within Target± 1σ, 96.43% of the population lied within Target ± 2σ and 99.58% lied within Target ± 3σ. It could be observed that majority of the values were on the higher side of Target which showed a tail (skew) on the left. Hence, it showed neagtively skewed distribution. The yield value obtained was 99.19% due to negative skew (Figures 5 and 6).

4. CONCLUSION

Control charts are powerful and user friendly statistical process tools that can be used for quality improvement of product. Control chart limits can act as “In- house” limits as they are narrower than Pharmacopoeial limits. SPC by control chart provides greater degree of assurance that variable of the product is within official limits when the product is released. Thus, in-house control chart limits decreases the consumer risk.

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