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Statistical Process Control Implementation in Pharmaceutical Industry for production process

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***Abstract*— The purpose of this paper is to understand the use of statistical process control (SPC) methodology by applying certain quality tool "X bar chart", and measurement of a process using process capability (Cp) and product performance or consistency (Cpk) in pharmaceuticals production process. The used case study was manufacturing process of tablets at IBN Hayan Pharmaceuticals Factory; data were collected through the production process of solid dosage form. A sampling plan was conducted to collect samples of finished products during the entire lot compression at equally spaced time intervals during the compression process of the production time; the critical measurement parameters studied in this paper was two parameters (weight (mg) and Hardness (Kp)).**

The monitoring graph "X Bar Graph" for the two parameters shows that the output data are within the specifications. Process capability (Cp) and product performance (Cpk) of finished product for the studied batches were greater than 1.0 and 1.33 respectively, which means process variation is too low, and production process is capable to produce 99.97% of products comply with specifications. Low variations measured in the studied batches, and then the process should be adjusted to perform at the target values. Generally, it can be concluded that the manufacturing processes are statistically capable repeatedly and reliably to produce finished product of predetermined quality. Therefore, the presented results demonstrated that SPC Monitoring methodology and tools are effective to reduce process variation then continuous improvement.

Keywords— good manufacturing practice (GMP), Statistical Process Control (SPC), Process capability, In Process Control (IPC).

I. INTRODUCTION (*PHARMACEUTICAL INDUSTRY*)

Pharmaceutical industry is characterized as the industry subject to the laws regulating all regarding this industry practices and methods of manufacture, and due to the content their manufacturing process of complexity and as the control and quality assurance of pharmaceuticals is the first duties of the pharmaceutical industry, and test ready-made material is no longer alone sufficient to ensure quality.

The efforts are being made for the application of "good practice for the manufacture of pharmaceutical" from the purchase of raw materials, production and control during manufacturing and control on the final product quality and release, storage, handling and distribution of the product, and most important of all documentation of those methods and practices, and is considered the rules and established Good Manufacturing Practice the spirit of regulations governing the pharmaceutical industry [1].

Control of quality during the manufacturing process (In-process control, IPC) might be done using Statistical Process Control (SPC), which is considered as an industry-standard methodology for measuring and controlling quality during the manufacturing process, It is also defined as a major statistical tool for monitoring of production process to make sure that it works stably. The stability of the production process is reflected by the conformance of the quality characteristics of its products to their designed requirements [2].

II. PRODUCTION PROCESS

A. Pharmaceutical manufacturing

Pharmaceutical manufacturing is a multi-steps process. Each manufacturing step is called a "Unit Operation" Each unit operation produces an intermediate with pre-determined quality specifications that will ensure the quality of the finished product. Pharmaceutical dosage forms, such as tablets, are widely used in today's drug product manufacturing. One of the unit operations in the process of producing tablets is the tablet compression machine. This equipment will apply compression force on the powder mixture containing the active pharmaceutical ingredient and other ingredients.

The result of the compression process is a solid entity known as a tablet. This tablet must have number of critical quality attributes that give the product its identity.

Tablet hardness, friability, disintegration, dissolution, content of active ingredient and dimensions are the important quality attributes to ensure the suitability of the tablet for the intended use.

To evaluate the tablet compression process for a new drug product. Pre-determined numbers of samples (subgroups) were taken at equally spaced time intervals during the entire lot compression process. Samples of tablets were taken at random from each subgroup and the hardness of each tablet was measured using tablet hardness tester. The test results are used to monitor the manufacturing process output that is more likely to cause finished product variability. Routine quality monitoring of a production process can be accomplished by process control charts.

In the production unit, there are many different types of defects that can occur, for example that the product is cracked, that there are errors in the design, or that information on the product is not correct [3].

B. Monitoring of Production Process

The monitoring of pharmaceutical production is the main and important process which can perform using control charts. The control chart is a graph used to study how a process changes over time. Data are plotted in time order. The control chart always has a central line for the average (X bar), an upper line for the upper control limit (UCL) and a lower line for the lower control limit (LCL), an upper warning limit (UWL) and a lower warning limit (LWL). These lines are determined from historical data. Diagram "X Bar Graph" is made with experimental data obtained from followed produced batches.

The "X Bar Graph" is used in statistic regulation of production and for monitoring [2].

The following equations and fig 1 are used for constructing "X Bar-Graph" as following:

X Bar = sum (xi / k), k = number of batches

Control limits (UCL, LCL) are ± 3% above and below X Bar

Alarm limits (UWL, LWL) are ± 2% above and below X Bar.

Types of regulation diagrams mention above are used in statistic regulation of production and for monitoring corresponding with GMP requirements [4], [5].

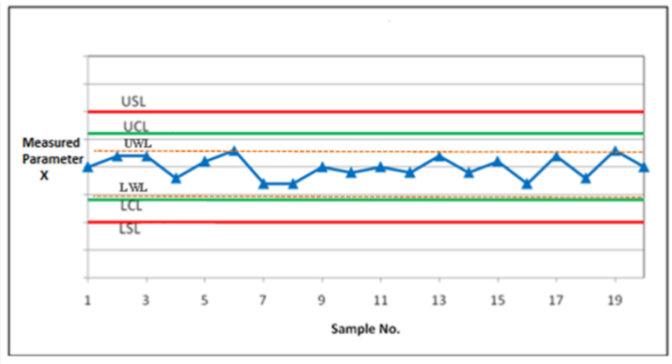

FIGURE-1: CONTROL LIMITS ON "X BAR GRAPH"

C. Process Capability

There are two formulae to calculate process capability:

(a) Process capability ratio (Cp), and

(b) Process performance index (Cpk)

Process capability, for a stable manufacturing process, is the capacity of the process to reach a certain level of quality. For a stabilized process in which factors affecting the standard deviation are properly controlled, process capability, as measured by the quality characteristics of the products of the process, is usually expressed as the mean value plus or minus three times the standard deviation [3].

The Process Capability Index (Cp) is expressed as a ratio to the specified value. It is used to quantitatively evaluate the adequacy of the process capability - whether the variation in the process is within the limits of the specifications.

Table 1 shows the interpretation of Process performance index (Cpk).

Cp= ((USL-LSL))/6S, where, S= Standard deviation

Cp is defined as process capable, and should be Cp ≥ 1 [4]&[6].

Cpk = min.{ ((USL-X))/3S , ((X-LSL))/3S }, where, S= Standard deviation

TABLE 1: INTERPRETATION OF CPK

Cpk	Evaluation	Assessment
Cpk > 1.33	Good	Process Capability completely meets specifications
1.33 ≥ Cpk <1.00	Acceptable	Process Capability does not completely meet specifications; process control should be continued
1.00 ≥ Cpk	Inadequate	Process capability inadequate; improvements should be made

Cpk index value means:

Cpk	Good products
0.33	68.3%
0.67	95.5%
1.00	99.7%
1.33	99.97%

III. RESEARCH METHODOLOGY

A. Methodology

The methodology used in this study is by collection of data during production process (In-process control) in Pharmaceutical Factory, where producing of Tablets process was chosen to ensure conformity of the GMP requirements. The chosen product was Paracetamol 500mg tablets, the measured specifications for three following success batches were written in the batch manufacturing record, and the samples were taken during the entire lot compression at equally spaced time intervals during the compression process of the production time. The numbers of sub-groups of samples were (10 samples), the critical measurement parameters are

weight (mg), Hardness (Kp), Friability (%) and Disintegration Time (min).
All the data generated from the process are plotted in SPC Control charts for monitoring the production process.
Analysis of the process capability using the critical parameters: weight variations and hardness have been done to show the capability of production process to produce product complying with the specifications.

B. Practical Study

The study is take place in a pharmaceutical factory IBN Hayan pharmaceutical factory "IH pharma" located at Tripoli-Libya. The factory is producing solid dosage form (Tablets). Products are manufactured and released as per Good Manufacturing Practices GMP.
The central problem to be solved by implementing SPC at "IH pharma" was to identify out-of-control situations and processes in the production. IPC data from "IH pharma" Batch Records were taken as a case study, the chosen product was paracetamol 500mg Tablets, samples for three followed batches were taken during the production process (In-Process control).

The obtained data were in real-time during compression of tablets process for each 5 minutes of production time, the number of sub-groups of samples were (10 samples).
In this paper the weight of tablets (mg) and hardness of tablets (Kp) as critical measurement parameters, IPC data then plotted on "X- Bar graph" Chart with pre-determined control limits are studied, Control limits are determined.

The IPC data obtained from the batch records are shown in Table (2).

TABLE 2: IPC DATA OF HAYADOL 500MG TABLETS

	Batch No. 1		Batch No. 2		Batch No. 3	
	Weight, mg	Hardness, Kp	Weight, mg	Hardness, Kp	Weight, mg	Hardness, Kp
Sample No. 1	609.6	11.5	607.6	10.8	597.3	7.8
Sample No. 2	610.8	11.1	612.2	10.9	596.3	8.8
Sample No. 3	611.1	10.9	611.8	11.4	599.7	10.1
Sample No. 4	615.9	11.7	606.0	11.6	502.1	10.9
Sample No. 5	617.1	11.8	609.1	11.5	598.9	10.2
Sample No. 6	613.6	12.2	609.5	12.1	600.3	10.3
Sample No. 7	628.1	10.8	615.6	10.4	597.9	9.8
Sample No. 8	612.6	11.2	606.8	10.8	604.0	11.5
Sample No. 9	610.8	11.9	608.9	11.3	603.4	8.5
Sample No. 10	610.5	11.8	606.8	9.8	601.8	10.2
Sample No. 11	615.4	10.6	611.1	10.1	598.9	9.5
Sample No. 12	613.2	11.1	615.6	10.9	600.8	9.7
Sample No. 13	609.9	11.7	610.5	11.4	603.8	9.9
Sample No. 14	610.0	9.9	611.9	10.5	598.4	8.7
Sample No. 15	616.7	10.3	610.9	10.1	604.3	9.1
Sample No. 16	615.9	11.8	613.7	12.0	601.2	8.9
Sample No. 17	616.3	10.1	612.2	11.9	601.7	9.0
Sample No. 18	613.8	10.9	609.7	11.6	603.7	8.5
Sample No. 19	616.7	9.1	611.7	10.9	601.2	8.7
Sample No. 20	614.4	10.5	610.1	11.2	598.3	9.6

IV. RESULTS AND DISCUSSION

A. Weight of Tablets (mg)

The procedure for calculation was made through manual collection and registration in a designed MS Excel spreadsheet the results are shown in Table (3).

TABLE (3) CALCULATIONS OF CONTROL LIMITS OF WEIGHT FOR PARACETAMOL 500MG TABLETS

	av. X	av.s	Av.R	Cp	Cpk
Batch Number 1	614.1	4.2	18.5	2.4	1.26
Batch Number 2	610.6	2.7	9.6	3.7	2.42
Batch Number 3	600.7	2.4	8.0	4.1	4.02
Average weight = 600mg USL = 630 mg LSL = 570 mg UCL = 618 mg LCL= 582 mg UWL = 612 mg LWL= 588 mg					

The calculated control limits of weight of paracetamol 500mg Tablets are plotted on Monitoring Figures 2,3,4

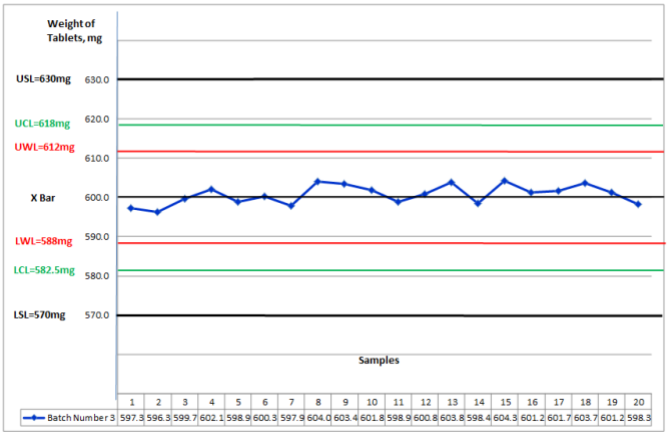

FIGURE-2: MONITORING GRAPH FOR WEIGHT (MG) – BATCH NUMBER 1

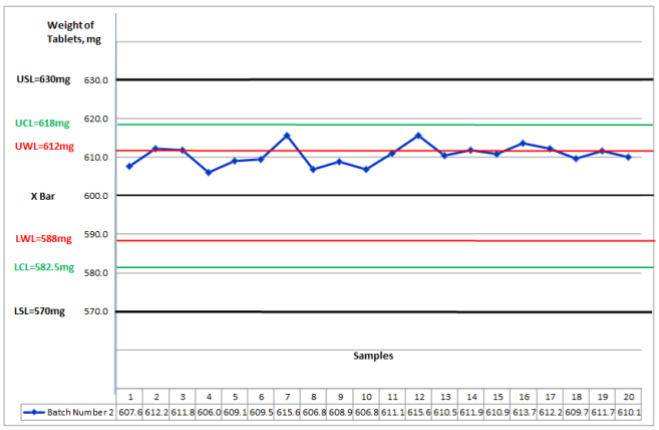

FIGURE-3: MONITORING GRAPH FOR WEIGHT– BATCH NUMBER 2

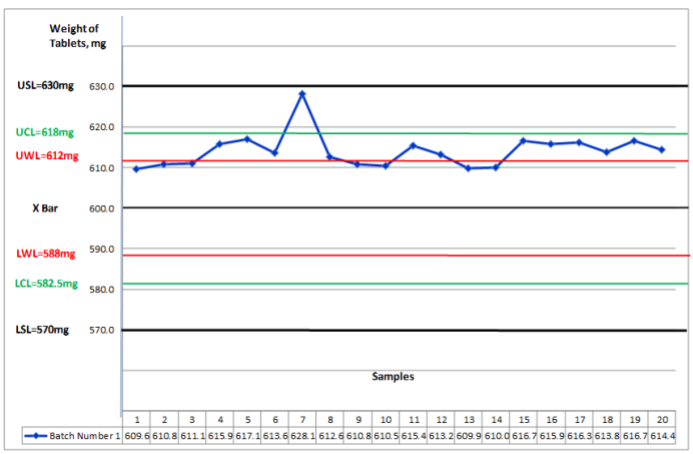

FIGURE-4: MONITORING GRAPH FOR WEIGHT– BATCH NUMBER 3

Figure (2) for control chart represents that sample No. 7 (628.1 mg) is upper the control limit (620 mg) and less than the upper specification limit (630 mg), and the other samples within the control limits. This results effect on the value of Cpk which was equal to 1.26, and lies between 1.0 and 1.33, which means 99.934 % of products are good quality and process need more control and adjustment to decrease the variations.

Figure (3 and 4) show samples within the control limits and 99.97% of produced products of related batches are good quality.

B. Hardness of Tablets (Kp)

The procedure for calculation was made through manual collection and registration in a designed MS Excel spreadsheet the results are shown in Table (4).

TABLE (4) CALCULATIONS OF CONTROL LIMITS OF HARDNESS (KP) FOR PARACETAMOL 500MG TABLETS

	av.X	av.s	Av.R	Cp	Cpk
Batch Number 1	11.0	0.8	2.3	1.3	2.06
Batch Number 2	11.1	0.7	2.3	1.6	2.51
Batch Number 3	9.5	0.9	3.7	1.1	1.24
USL = - LSL = 6.12 Kp					

The calculated control limits of hardness are plotted on Monitoring Figures 5,6,7.

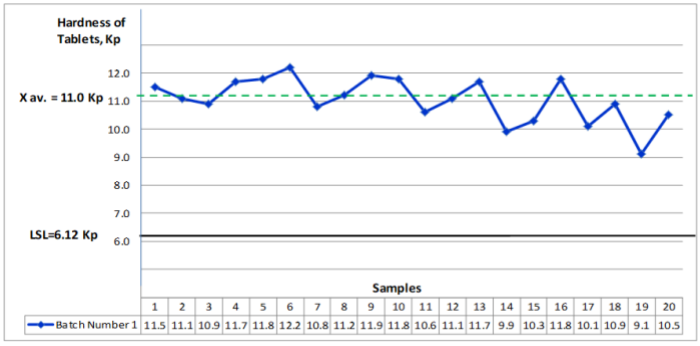

FIGURE-5: MONITORING GRAPH FOR HARDNESS– BATCH NUMBER 1

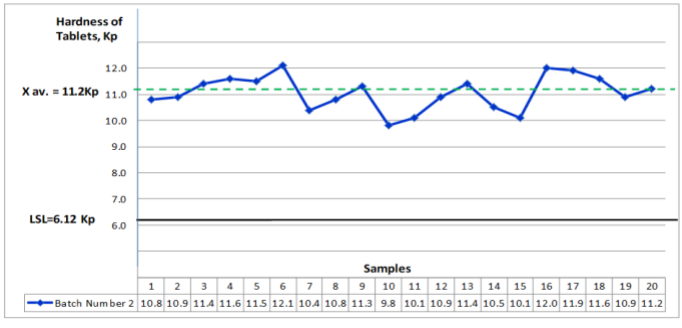

FIGURE-6: MONITORING GRAPH FOR HARDNESS– BATCH NUMBER 2

Figure (5) and (6) show all samples are above the lower specification limit (6.12 Kp) and the value of Cpk is more than 1.33, which means 99.97 % of products are good quality and variations are very low.

Figure (7) shows variation in Hardness and Cpk values is (1.24) which is lies between 1.0 and 1.33, which means 99.916% of products hardness are good and process need more control and adjustment to decrease the variations. Generally, we consider the manufacturing process is in control.

V. Conclusions and recommendations

To achieve high level of product quality in pharmaceutical industry, it must be follow the Good Manufacturing Practices regulations, monitoring of processes is one of the requirements by GMP, monitoring should be done using SPC tool (control charts) and measurement of process using process capability (Cp) and product performance or consistency (Cpk).

If Cp greater than 1.0 and Cpk greater than 1.33, which indicate that process is capable to meet specifications. In this paper the manufacturing process for producing of paracetamol 500mg tablets at IBN Hayan pharmaceutical factory had been measured and analyzed using statistical process control methods and found that the production process is statistically capable repeatedly and reliably to produce finished product of predetermined quality.

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REFERENCES

[1] WHO Guidelines on good manufacturing Practices (GMP), available on:
http://apps.who.int/medicinedocs/_ documents/s14215e/s14215e.pdf .

[2] Berardinelli Carl , “A Guide to Control Charts ". iSixSigma newsletter. (Monday, Feb. 22, 2016): available on http://www.isixsigma.com/tools-templates/control-charts/a-guide-to-control-charts/

[3] International Journal of Pharmaceutical and Life Sciences: Process Capability Analysis in Pharmaceutical Production by Mohammed Raihan Chowdhury, ISSN 2305-0330 Volume 2, Issue 2: March 2013.

[4] M Process Capability Analysis, available on: http:\\www.isixsigma.com\st\proces_capability

[5] X bar and R CHARTS: Theoretical Control limits for charts, available on: http:\\ www.isixsigma.com\offiste.asp?A=Fr&U.1.htm1

[6] e-Handbook of Statistical Methods, available on: http://www.itl.nist.gov/div898/handbook/, date: 02 March 2013.

[7] Journal of GXP Compliance: GMP Audit by Brandt C., 2014, Vol. 18 Issue 3

[8] PharmaTutor Magazine: A Review on Good Manufacturing Practice (GMP) for Medicinal Products by Chaudhari V., 2014, Vol. 2, Issue 9.

FIGURE-7: MONITORING GRAPH FOR HARDNESS– BATCH NUMBER 3