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Short Communication

Application of statistical process control for spotting compliance to good pharmaceutical practice

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For the release of pharmaceutical products into the drug market; most of the pharmaceutical companies depend on acceptance criteria - that are set internally, regulatory and/or pharmacopeially. However, statistical process control monitoring is underestimated in most quality control in cases; although it is important not only for process stability and efficiency assessment but also for compliance with all appropriate pharmaceutical practices such as good manufacturing practice and good laboratory practice, known collectively as GXP. The current work aims to investigate two tablet inspection characteristics monitored during in-process control viz. tablet average weight and hardness. Both properties were assessed during the compression phase of the tablet and before the coating stage. Data gathering was performed by the Quality Assurance Team and processed by Commercial Statistical Software packages. Screening of collected results of 31 batches of an antibacterial tablet - based on Fluoroquinolone -showed that all the tested lots met the release specifications, although the process mean has been unstable which could be strongly evident in the variable control chart. Accordingly, the two inspected processes were not in the state of control and require strong actions to correct for the non-compliance to GXP. What is not controlled cannot be predicted in the future and thus the capability analysis would be of no value except to show the process capability retrospectively only. Setting the rules for the application of Statistical Process Control (SPC) should be mandated by Regulatory Agencies.

Keywords: Statistical process control (SPC). In-process control. GXP. Film coated tablet. Fluoroquinolone. Capability analysis. Pharmaceutical practice.

INTRODUCTION

The core value around which pharmaceutical industry is basically centered is the delivery of medicinal products which fulfill five criteria namely: Safety - Identity -Strength - Purity - and Quality (SISPQ) (Welty, 2009). The deficiencies in products quality delivered to final customer may not be obvious to the consumer, so the Quality Team is a crucial defense line that protects both patients and manufacturers from consequences of delivering non-conforming drug products to the market. However, the problem exacerbation may be due to its effect(s) on employees' morals and attitudes due to deficiency in quality. Thus, if the quality concept is not communicated efficiently within the organization, the consequences on the impacted products would be devastating (Asotra, Cossin, Yacobi, 2012).

For any firm to work with high-quality standards level, an efficient Quality Control (QC) system must be implemented (Spiridonică, 2011). Since achieving highest levels of quality standards are hindered by the extent of variability, thus, the main value of Statistical Process Control (SPC) resides in reducing the variability in the manufacturing process (Spiridonică, 2011). The concept of the continuous improvement in any organization by reducing variability is critical for both SPC and overall Quality Management (Ciobanu, Schreiner, 2002).

Due to above-mentioned challenges, present work aims to investigate the current state of control for a pharmaceutical product manufactured in a new pharmaceutical firm. Furthermore, monitoring the process stability would provide assurance on future process yield consistency. The study also focused on

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detecting the compliance of manufactured product to best pharmaceutical practice which may be referred to, here, as GXP through SPC. The study scope will cover two inspection properties of a pharmaceutical product viz. the average weight and hardness of tablet. By using SPC, the current state of manufacturing control can be evaluated for monitoring of both characteristics. Moreover, the current state of the process stability would determine the consistency and steadiness of inspected characteristic. This is considered a crucial integral part of product manufacturing good practices. Accordingly, the product value could be evaluated through the degree of compliance with GXP.

MATERIAL AND METHODS

A non-sterile manufacturing pharmaceutical plant was established in the Industrial Zone at South Delta region in Egypt. The plant has begun launching products of class D production area for solid dosage forms (Eissa, 2016a). During 2016, 31 batches of film coated tablets based on Fluoroquinolone - as an active pharmaceutical ingredient (API) - were manufactured, tested and released according to the specifications in Ministry of Health (MoH) product registration.

The current study is part of a large project covering different inspection characteristics of a variety of the firm's medicinal dosage forms. The product is a film coated tablet that is composed of Levofloxacin (API: Broad spectrum antibiotic of Fluoroquinolone class (Briggs, Freeman, Yaffe, 2012; levoflaxin, 2017), hydroxy propyl methyl cellulose (Disintegrant), crospovidone (Disintegrant), Avicel PH 102 (Filler), sodium stearyl fumarate (Lubricant) and coating material (Coating film) (Eissa, Mahmoud, 2015; Sodium Stearyl Fumarate, 2017).

The manufacturing process includes the following steps: dispensing and weighing components from warehouse, blending, compaction followed by last blending step then compression, coating, blistering and packaging finally in secondary package to be transferred to the finished products warehouse. A process that is very common in solid oral dosage forms manufacturing and similar aspects have been discussed before by some field experts (Harbir, 2012; Mulla, 2015).

Two inspection characteristics were assessed in the production process during tablet core compression phase, namely: average weight and hardness. Results were collected from In-Process Control (IPC) monitoring logs and arranged batch-wise in Microsoft Office Excel 2007. Data were subjected to statistical analysis using GraphPad Prism Version 6.01 software for Windows. The analysis was performed as described in software manual guide (GraphPad Prism User Guide, 2015). Distribution identification and analysis was conducted using XLSTAT Version 2014.5.03 (Eissa, 2016b).Box-and-Whisker Plots and control charts were constructed using Minitab® Version 17.1.0 (Minitab 17, 2013).

RESULTS AND DISCUSSION

SPC tools and techniques have become an essential part of quality monitoring and improvement system in many industries including the pharmaceutical manufacturing field. The first step involved an overview on results, its pattern and data homogeneity. Analysis of results during data mining showed that the average tablet weight in the 20th batch was exceedingly high outlier (although not Out-Of-Specification (OOS)) value "692.13 mg" by Robust regression and Outlier removal method (ROUT) (Q = 1.0%) test during trending average weight results(GraphPad Prism User Guide, 2015). This unexpected result highlighted the need to further analyze to elucidate reason for such observation. On the other hand, hardness test results did not show any outliers preliminarily using GraphPad Prism. On the same line, Box-and-Whisker diagrams illustrated in Figure 1 confirmed the absence of outliers (indicated by absence of asterisks "*"). Moreover, they showed the pattern of data distribution with a little degree of skewness towards the lower side (Lane, 2017). Minimum, 25% percentile, median, 75% percentile and maximum values for average weight and hardness were 644, 654, 660, 665, 669 and 15, 16, 16, 17, 18.

The second step focused on the determination of the data distribution and degree of normality which was important in the interpretation of the trending charts in the study. Removal of abnormally high result from average weight data has improved normality by Anderson-Darling (AD) test from P =0.023 to P =0.110 (Support.minitab.com, 2016). Interestingly, distribution fitting test showed that Weibull (2) distribution is the closest with P =0.982 (The Weibull Distribution, 2017). In contrast, hardness data still demonstrated that normal distribution is the closest fit with P =0.9692. The Mean Value ± Standard Deviation (SD), skewness and kurtosis of average weight and hardness were 659±6.2 mg, 16±0.82 Kilopond (Kp), -0.65, -0.20 and -0.31, -0.88, respectively. The coefficient of variation and the geometric mean were 0.94%, 659 and 5.11%, 16, respectively. Figure 2 and 3 demonstrated normality of both average weight and hardness visually, respectively, using normal probability plot (The Anderson-Darling Statistic, 2017). Thirdly, capability histogram was

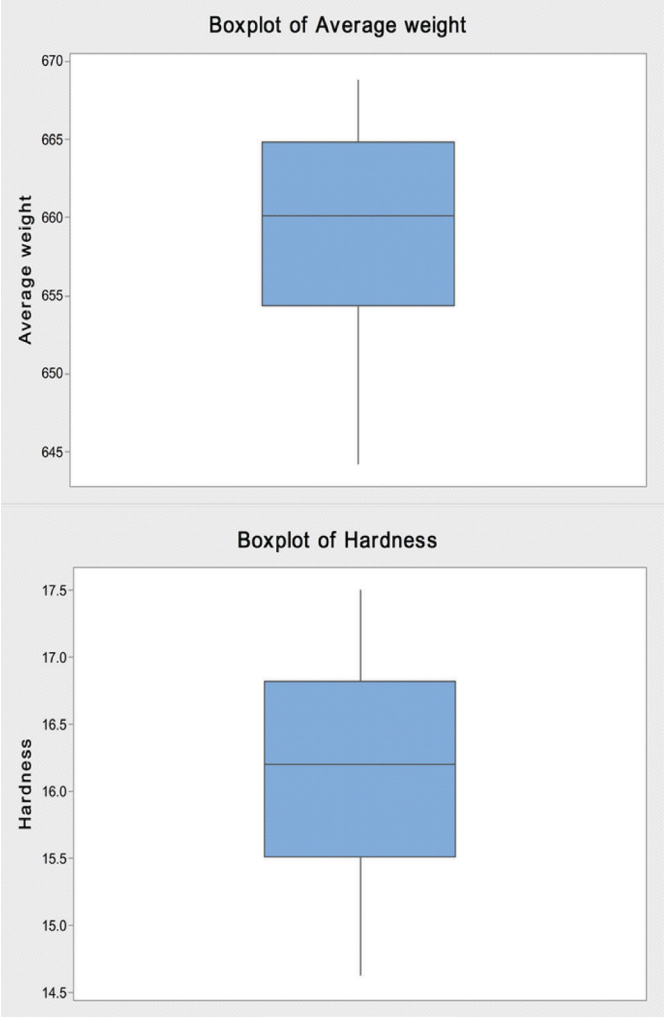

FIGURE 1 - Box Plot diagram showing the pattern of data distribution for average weight and hardness as part of IPC tests during the compression process.

interpreted for both of the inspection properties in order to determine the location of normally distributed process between specification limits (SLs). In addition, histograms were not centered within SLs and data was found to be shifted towards the lower average weight limit. While results of hardness strongly shifted towards the upper limit (Minitab 17, 2013).

Examination of the constructed process behavior (control) chart was inspected - after histograms examination to monitor the process. Shewhart charts were constructed for different types of data with a certain degree of normality using Individual-Moving Range (I-MR) chart as demonstrated in Figure 2 and 3. Normality assumption was confirmed to avoid errors in alarm detection while constructing Shewhart charts. I-MR is actually composed of two charts: I chart that determined the process state of control mean and MR chart which showed the process variation stability. Surprisingly, none of the inspected parameters showed acceptable stability, consistency or efficiency in the process (Smartersolutions.com, 2017). Interestingly, although the process variation (from MR charts) was stable (except for one point in hardness), the process center (I charts) was in "Out-of-Control" state especially in average weight. The assignable causes of fluctuations (indicated by batches represented in red dots) should be isolated from normal processes with common cause variations (Martz, 2013). Moreover, both processes are not centered and showed drifts toward either of the border specification limits with possible future excursions. This case was especially evident with hardness in capability analysis. Accordingly, capability plots have no value and may indicate past performance only but cannot provide future prediction unless the processes instability factors were corrected by Corrective Action and Preventive Action (CAPA) (Qimacros.com, 2017). Since there was no subgroups for each point, the last 25 observations in Figure 2 and 3 are the same as in the last ones in I charts. Further investigation is required to figure out and correct the source of non-GXP activities which might stem from the manufacturing and/or IPC activities.

The current study demonstrated the need to establish an official requirement for SPC in pharmaceutical monitoring as a part of routine quality system through Regulatory bodies to solve the non-compliant activities concurrently and immediately rather than retrospectively. SPC provides strong control and verification of newly established operation efficiency and the needed adjustments if the process is not working satisfactorily. To conclude, the pharmaceutical dosage forms may meet the specification limits required for the product release, while hiding signs of future excursions that may turn into true OOS. Moreover, SPC provides visual evidence of process stability accompanied with GXP.

Accordingly, it could be concluded from previous study that the inspection characteristics monitoring of pharmaceutical products should take into consideration each of the following:

1. SPC could provide a visual measure of specific procedure compliance with GXP.
2. The importance of official regulatory enforcements for implementation of SPC within pharmaceutical industry especially in developing countries.
3. Monitoring overall manufacturing cycle performance of product rather than reliance on product release specifications only may show the gap between delivered into market product, its true manufacturing quality conditions and the environment within which it has been manufactured.

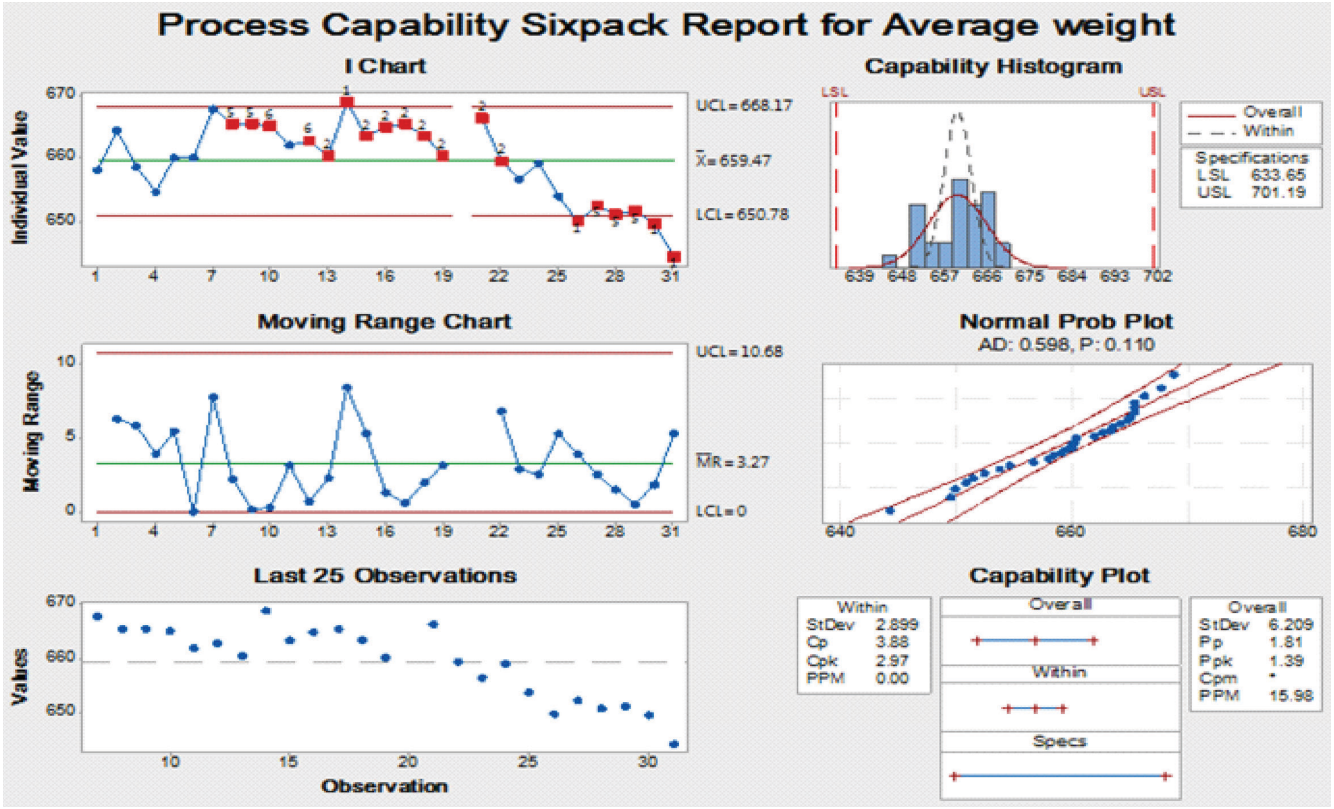

FIGURE 2 - Statistical control monitoring of average weight test showing out-of-control points as red dots.

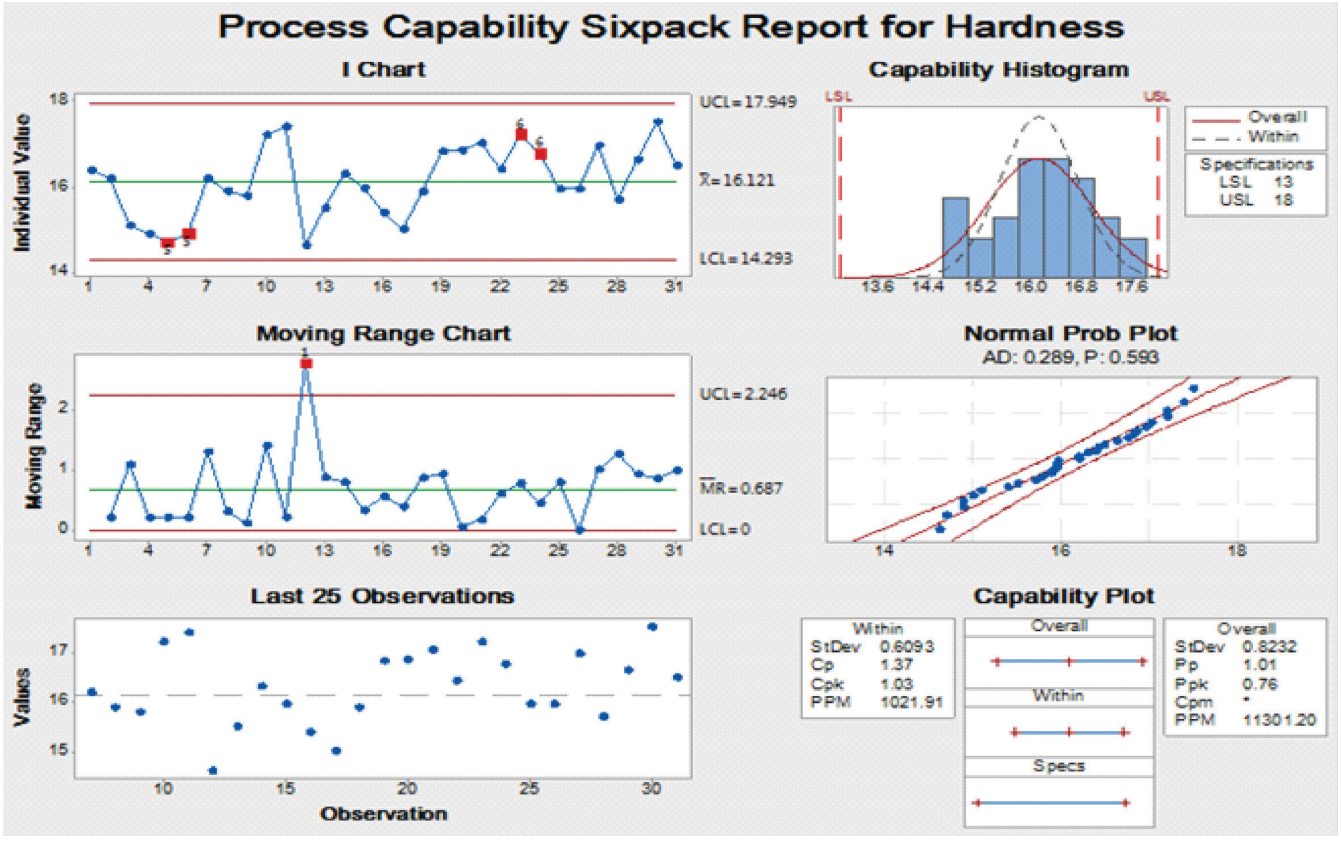

FIGURE 3 - Statistical control monitoring of hardness test showing out-of-control points as red dots.

4. The application of the current method is simple and saves time using a statistical software package, yet its full potential in product quality process monitoring is crucial.

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