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RESEARCH ARTICLE

TRENDING PERSPECTIVE IN EVALUATION OF INSPECTION CHARACTERISTICS OF PHARMACEUTICAL COMPOUND: COMPARATIVE STUDY OF CONTROL CHARTS

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Abstract

Background and objectives: The quality and efficacy of the pharmaceutical medicinal product are of paramount importance to the patients. Reproducibility and consistency of the properties of the dosage form start with the constituting ingredients either active or inactive. The present work provides an approach for the trending of one of the crucial inspection characteristics of a well-known excipient that is commonly used as a disintegrant of a water-insoluble synthetic cross-linked Polyvinyl Pyrrolidone (PVP). Establishing manufacturing criteria and quality limits should be assessed from the beginning level of the project using exploratory process-behavior plots.
Materials and Methods: This study involved an assay of the initial 16 batches of the manufactured 1-ethenyl pyrrolidine-2-one expressed as a dried substance using a standard analysis method according to British Pharmacopoeia (BP). Exploratory Shewhart charts were plotted after preliminary distribution identification using Statistical Process Control (SPC) software. Based on the goodness of fit test results, the most appropriate assumed distribution was implemented in drawing the Individual/Moving Range (I/MR) control charts.
Results: The goodness of fit study and probability plot showed that the most close-fitting to the data dispersion pattern was Johnson transformation to the normal spreading, smallest extreme value and Weibull distribution, respectively. While there were no alarms that could be detected from the process mean and the variability charts, further improvement is required from the supplier side to meet the benchmark minimum limit threshold, in addition, the process mean was not centered but shifted towards the Upper Control Limit (UCL).
Conclusion: Implementation of SPC techniques is crucial in the modern competitive healthcare industry. Trending charts play a pivotal role in this perspective. They provide a quantitative estimation for the current situation and the actions needed for the future improvement of the monitored characteristic.
Keywords: Capability plot, control charts, Johnson transformation, probability plot, smallest extreme value, Weibull.

INTRODUCTION

In the world of competitive healthcare and the pharmaceutical industry, many companies and firms compete in the drug and medicinal products market[1-3]. However, safety, quality and efficacy come as the first-place priority of the patient Health[4-6]. Medicinal ingredients either active or inactive should be the cornerstone for the standard quality before the analysis of the inspection properties of the finished medicinal dosage forms.

Implementation of the Statistical Process Control (SPC) techniques are now widely used and considered essential in all pharmaceutical firms to achieve a high level of predictable and acceptable quality[7-9]. One of the most pivotal SPC tools is the Shewhart plot[10]. It has vast applications in many industrial and non-industrial areas to assess and control processes and inspection characteristics[11-15]. The manufacturers of the raw chemicals of pharmaceutical grades have expanded worldwide making them easy to be attained in the retail markets and brokers anywhere[16]. Nevertheless, sustainable quality assurance of the expected chemical and physical properties is of paramount necessity to guarantee the current and the future merit of the pharmaceutical products.

There are growing trends in the number of chemical manufacturing facilities, notably in the developing

nations. The Good practices in various fields (GxP) status of them including the medicinal and healthcare sectors are questionable[17,18]. Good Manufacturing Practice (GMP) could be projected into the quality of the final product[19]. Hence, an organization with the right quality concept in mind throughout the whole firm would yield products with acceptable, stable and predictable properties with minimal risk of failure.

In a time of crisis, there is a great possibility of witnessing degradation in the quality of goods that are available from the brokers, wholesalers and market retailers to meet the demand of the customers with low prices at the expense of the essential quality inspection characteristics. Due to the emphasized challenges, the current study sought to assess the excellence and goodness of a selected excipient that is commonly incorporated in pharmaceutical preparations from chemical manufacturing companies. The study will focus on an important test that is officially considered one of the critical inspection properties of inactive material.

MATERIALS AND METHODS

A chemical manufacturing plant of raw materials of pharmaceutical grade was assessed for the quality of the manufacturing output[16,17]. Sixteen batches of one of the common excipient materials were investigated for the assay result trend[16,17].The inactive material - which is commonly known to be used as a thickening agent, solubility enhancer, disintegrant and emulsifier – is an insoluble polyvinyl pyrrolidinone polymer that is crosslinked or Polyvinylpyrrolidone (Crospovidone) with the chemical formula $(C_6H_9NO)_n$.

According to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature, it is named 1-Ethenylpyrrolidin-2-one[20]. Each manufactured batch was subjected to the analysis using the standard official method of the British Pharmacopoeia (BP)[21]. The assay limit is 11.0-12.8 % of nitrogen based on dried substance[21]. The preliminary assay data was analyzed using Minitab version 17.0 to screen for the distribution fitting and to construct an appropriate SPC examination profile[22-25]. Based on the output results, the initial state of control could be determined from the control charts, capability analyses and histograms.

The assay was conducted as follows: 0.100 g of the substance to be tested (in milligrams) was introduced to a combustion flask along with five g of a mixture that included one g each of copper sulfate pentahydrate R, titanium dioxide R, and di-potassium sulfate R, as well as three glass beads[21]. To rinse away any particles that stuck to the neck and into the flask, a very small amount of water R was employed. Sulfuric acid R (seven milliliters) was added and allowed to drip down the inner wall of the flask[21]. The solution was gradually heated in the flask until it took on a clear, yellowish/green hue and the interior wall of the flask was free of carbonized material. Then, the flask was heated for an additional 45 minutes.

The contents of the flask must be cautiously poured into 20 mL of water R after it has cooled. Attaching the flask to the distillation apparatus which has previously been cleaned by passing steam through it is necessary[21]. To submerge the bottom end of the condenser tube in the absorption flask, enough water (R), 0.15 mL of a bromocresol green/methyl red solution (R), and thirty milliliters of a 40 g/L boric acid solution (R) must be added[21]. A funnel should be filled with thirty milliliters of strong sodium hydroxide solution R. The funnel should then be gently rinsed with ten milliliters of water R. Immediately after, the rubber tube clamp needs to be closed, and the steam distillation process needs to be initiated in order to extract 80-100 milliliters of distillate.

Following the removal of the absorption flask from the lower end of the condenser tube and a quick wash with some water R, 0.025 M sulfuric acid was added to the distillate until the color of the solution changed from green to pale greyish blue to pale greyish red-purple[21]. Any necessary corrections were to be made after performing a blank measurement.

Statistical analysis

Distribution identification was done at 95 % Confidence Interval (CI) and α 0.05; best fitting spreading plot was verified using the Anderson/Darling (AD) test. Raw data that fails to follow any definite spreading was subjected to transformation by the Johnson family algorithm for normalization and if it passes the normality test then it can be subjected to further analysis. The most applicable types of distributions were applied for drawing the variable process-behavior charts with the associated capability plots and capability histograms. All the computations and graphing were done using statistical software.

RESULTS AND DISCUSSION

This project is part of a total examination of the organization to achieve the Total Quality Management (TQM) goals of the chemical plant[26,27]. The technique of total quality management (TQM) continuously detects, reduces, or eliminates production errors[27]. It ensures that employees get the newest training possible, speeds up supply chain coordination, and raises customer satisfaction[27]. To achieve complete quality management, all parties involved in the manufacturing process must be held accountable for the overall quality of the final product or service.

Detailed dispersion pattern of the dataset using probability plots are shown in Figure 1 and Figure 2. The goodness of fit test demonstrated that only three distributions are valid in the following descending order: Normal (after Johnson transformation), smallest extreme value and Weibull. The selection was based on Anderson-Darling (AD) the goodness-of-fit figure probability charting and the p-values.

A probability called the p-value assesses the strength of the evidence against the null hypothesis[28]. The null hypothesis for an AD test is that the data are distributed as expected[29]. Lower *p*-values thus offer more proof that the data do not fit the distribution. The preliminary exploratory Individual/Moving Range (I/MR) process behavior charts in Figure 3, Figure 4, and Figure 5 showed stable variations and process means according to the selected types of the best-fitting distributions.

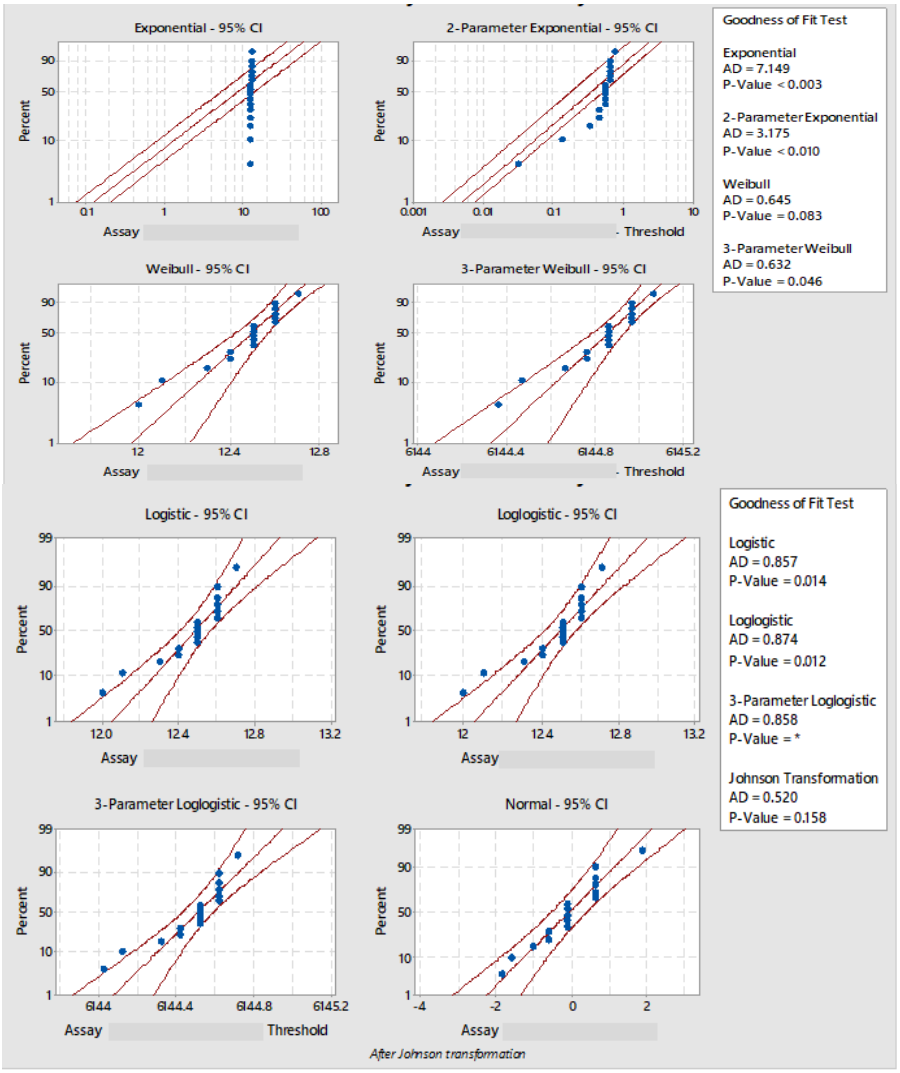

Figure 1: Probability distribution identification showing the goodness of fit test to exponential, two-parameter exponential, Weibull, three-parameter Weibull, logistic, log logistic, three-parameter log logistic and Johnson transformation to normal distribution.

Each corresponding dispersion was acceptable according to the probability plot[30,31]. Moreover, the capability histograms illustrated that the spreading of data was confined within the Lower Specification Limit (LSL) and the Upper Specification Limit (USL) [32]. In addition, the bins' dispersion frequency is close to the hypothetical presumed underlying distribution assumption[33]. It is evident that the process average is not centered in the middle of the specification window, instead it showed that the preliminary results are all above the centerline risking an excursion above the upper threshold. The sample mean± the overall standard deviation was approximately ≈ 12.5±0.19. In the capability analysis, the width of the inspection characteristic variation i.e., the Voice of Process (VoP) should be less than the Voice of Customer (VoC) [34]. P_{pk} is the index for performance centering[35]. It gauges the degree to which the data is centered inside the specified bounds. The resultant values in Figures 3, 4 and 5 lie within 1.00 and 1.33[36].

This is in the middle of the road and more improvement should be made to achieve the benchmark target value. On the other hand, P_p is the index of performance[35,36]. It gauges the degree to which the data could fit inside the specified bounds (USL, LSL)[35,36]. Nevertheless, it doesn't matter if it is centered within the boundaries window. In this case, it is obvious that the inspection characteristic of the assay results yielded satisfactory results in terms of the overall capability examination study. Z. bench (overall) is the percentile that converts the predicted probability of process defects to an upper tail probability on a standard underlying assumed distribution[37]. It is computed using the overall standard deviation and is dependent on the overall performance of the process[37]. While Z.LSL was acceptable, Z.USL showed values below Z. bench.

The predicted percentage of parts outside of the specified limitations is the percent total for expected overall performance. Calculating the expected value involves utilizing the total standard deviation. The probability that the measurement of a randomly chosen portion from the overall process distribution is beyond the specified bounds is the percentage total for predicted overall performance.

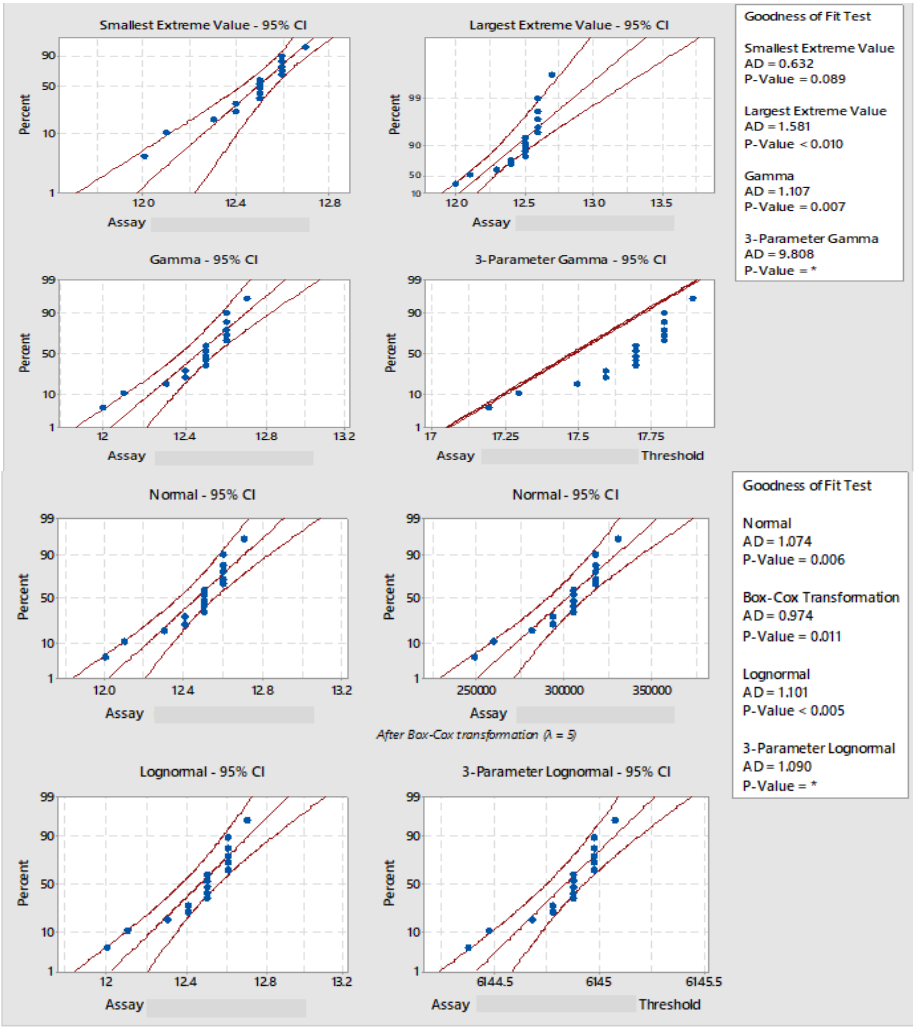

Figure 2: Probability distribution identification showing the goodness of fit test to smallest extreme value, largest extreme value, gamma, three-parameter gamma, normal, Box-Cox transformation to normal distribution, lognormal and three-parameter lognormal.

Based on the overall variation of the monitored process, the percentage above USL is used for predicted overall performance to estimate the percentage of nonconforming products that might be expected to be above the upper specification limit[38]. The actual process performance that the inspection property experiences over time is indicated by the overall performance values[38]. In comparison to the maximum specification limit, lower values of the percentage over USL indicate more process capability. Few or no parts should have measurements that are higher than the highest limit of the specification. The same could be extrapolated for the percentage below LSL.

It should be emphasized that establishing statistical quality monitoring from the beginning of the manufacturing process for chemical production is a mandatory activity that should not underestimated to ensure obtaining raw materials with stable, predictable and conforming inspection properties indicating a Good Manufacturing Practice (GMP) during the production processes[39]. It is important to implement GxP for any reputable company to take the lead in any competitive market where the common acronym for quality standards and recommendations that are considered to be "good practice" is GxP[40]. The different areas it can be applied to are represented by the "x". GxP is an abbreviation that is frequently used to describe a group of quality standards. The quality of the single components would be reflected in the functioning values of the final dosage forms. This is crucial when considering the health and life of the patients in the world of ever-growing populations of sick individuals.

Limitations of the study

While monitoring and control of the inspection properties could be ensured by the above-implemented technique, transformation might change the original shape of the time series plot which could make the extrapolation during investigation more difficult and challenging. Also, more data (and hence more batches) are required to establish solid criteria through the control charts rather than being exploratory in the initial stages.

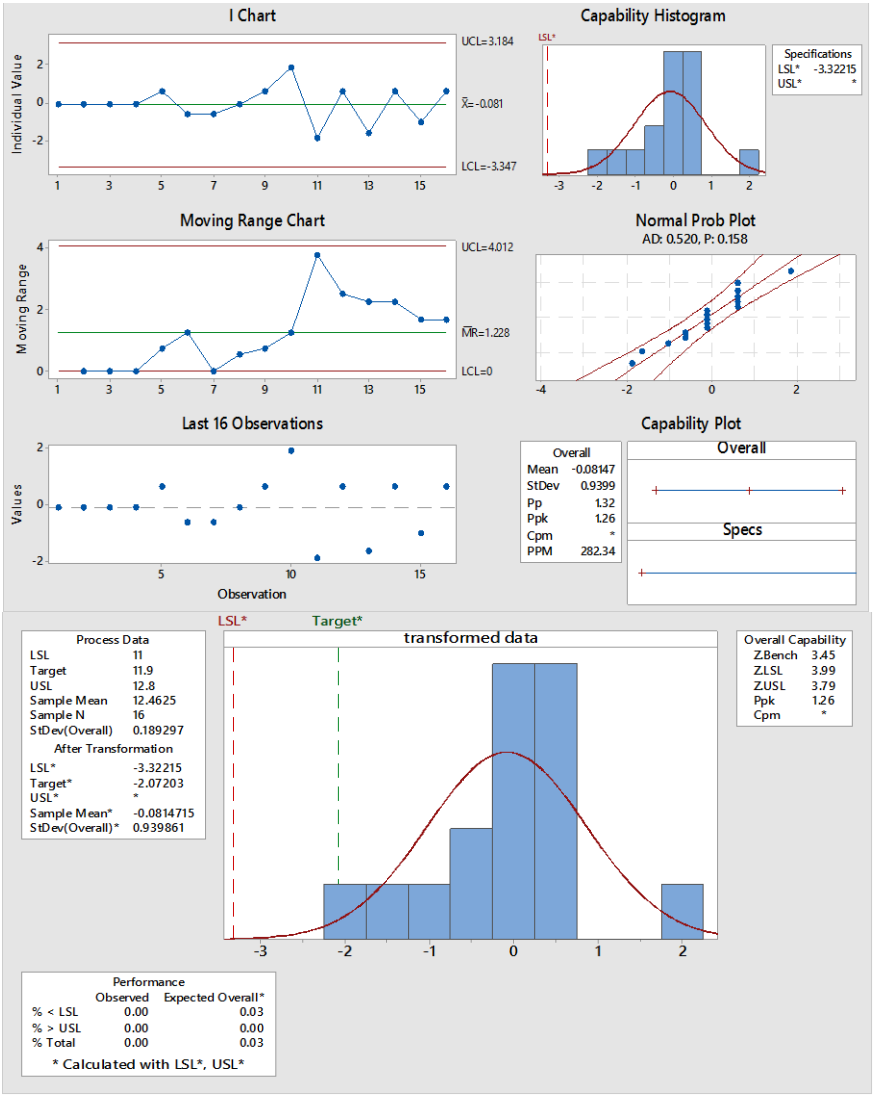

Figure 3: Process capability six-pack of the assay using Johnson transformation to the normal distribution using transformation function $\gamma + \eta \ln [(x - \varepsilon)/(\lambda + \varepsilon - x)]$ for Johnson family distribution with the variable bounded {B}(SB) with a range of $\eta, \lambda > 0$, $-\infty < \gamma < \infty$, $-\infty < \varepsilon < \infty$, $\varepsilon < x < \varepsilon + \lambda$.

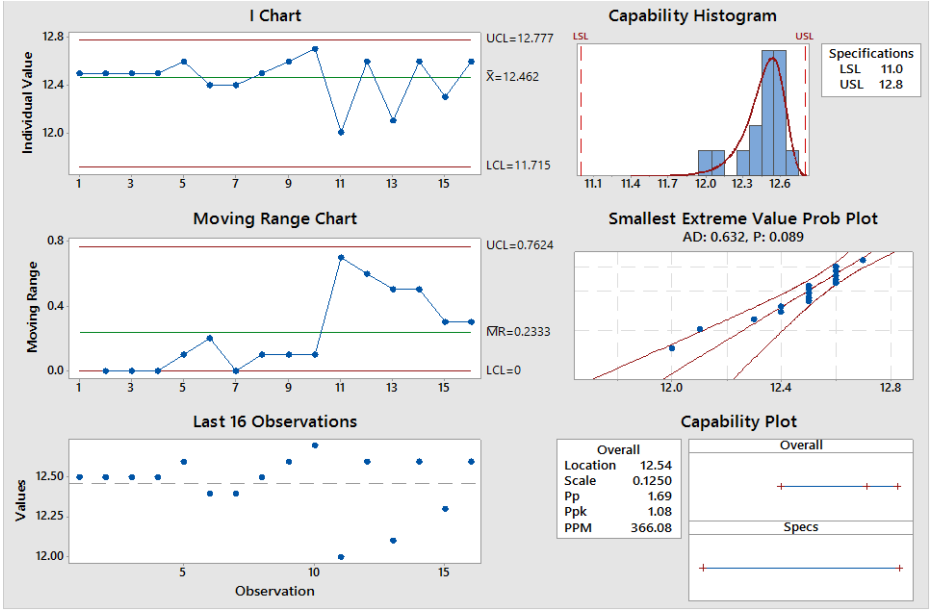

Figure 4A: Process capability six-pack of the assay using smallest extreme value distribution.

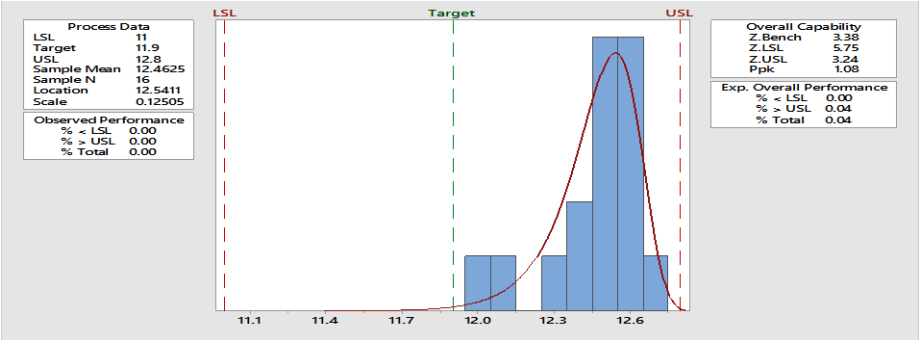

Figure 4B: Process capability six-pack of the assay using smallest extreme value distribution.

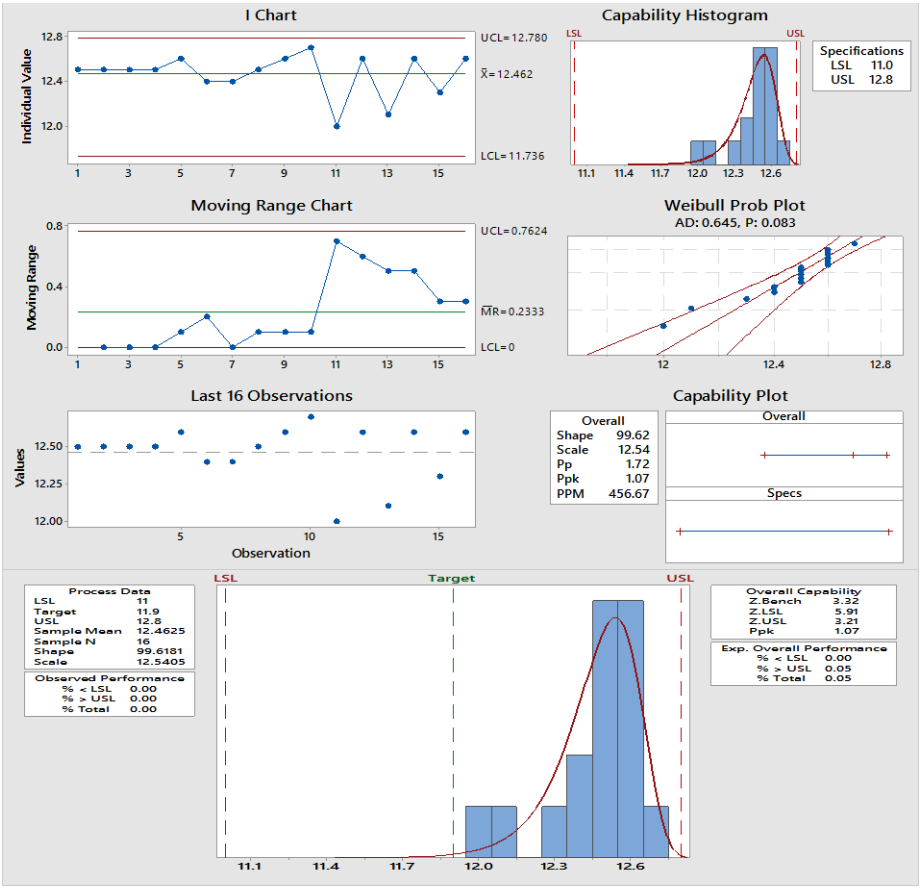

Figure 5: Process capability six-pack of the assay using Weibull distribution.

CONCLUSIONS AND RECOMMENDATIONS

Process-behavior plots based on the non-normally distributed datasets showed the quality of the manufactured raw material did not demonstrate out-of-control states between the successive batches. However, the process capability monitoring showed that the performance needs improvements and tightening in the variations of the inspection characteristic (assay) between consecutive products is essential to achieve better performance index level.

Accordingly, the mean of the process should be brought close to the center to avoid any risk of out-of-control results above the upper limiting threshold in the future. Further research studies with other inspection characteristics of the pharmaceutical raw material should be conducted and other medicinal ingredients produced by the manufacturer should be included.

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None to declare.

AUTHOR'S CONTRIBUTION

Eissa ME: Writing original draft, review, methodology, data curation, literature survey, editing.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTERESTS

None to declare.

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