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# Statistical Process Control Implementation in Inspection of Active Medicinal Compound Quality: A Model of First-Generation Antihistaminics

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**ABSTRACT**

This study is part of a large project that includes surveying and screening medicinal compounds manufactured by chemical and pharmaceutical plants, notably in Asian countries and exported to developing countries. The current investigation focused on the active pharmaceutical ingredients (API) of one of the first-generation antihistamines of ethanolamine class known as 2-(diphenylmethoxy)-N,N-dimethylethanamine hydrochloride according to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature. Harmonization of the specifications and analysis criteria were harmonized and all raw materials were claimed to be complying with the British Pharmacopoeia (BP) according to the manufacturers. Accordingly, all testing procedures were done according to the official standard methods detailed in the monograph of the chemical molecule. The selected tests were acidity or alkalinity, related substances, loss on drying (LOD), sulfated ash and assay (based on dried substance). Datasets were gathered and processed using Statistical Process Control (SPC) software. Preliminary data examination was done using box plots and distribution identification for screening the best-fitting one. With the exception of the assay, all results showed a failure to follow specific dispersion. All raw data failed normality tests (Anderson-Darling test, $P < 0.05$). Accordingly, the output of the tests was adjusted to fit the application of the attribute charts. Laney modification was used to correct data dispersion. The correction factor acidity/alkalinity, impurity A, any other impurities, total impurities, LOD and sulphated ash were 1.003, 1,18568, 1.21158, 1.71165, 1.44613 and 0.883609, respectively. Control chart for normal data was used after Johnson transformation following equation $0.558 + 1.211 \times \text{Ln}((X - 98.929)/(101.13 - x))$. It should be noted that even when there was no out-of-specification there were several out-of-control points that highlight the necessity for appropriate investigation and correction for assignable causes of variations between batches. There should be governmental enforcement of industrial SPC rules for the quality and safety of the supplied medicinal substances from the chemical manufacturing companies.

## INTRODUCTION

In a globe of ever-growing healthcare and pharmaceutical complexity, numerous companies and enterprises contend in the medicine and medicinal products market (Eissa, 2020a, 2021; Eissa et al., 2016). Still, safety, quality and effectiveness come as the first-place precedence for the health of the final users (Liang & Mackey, 2011; Anonymous, 2019; Eissa et al., 2022). Medicinal constituents, either active or inactive, should be monitored and controlled for standard quality before the analysis and examination of the inspection properties of the final healthcare and medicinal finished product form. This should be stressed not only by the original manufacturer and the final customer but also by the regulatory industrial governmental agencies.

The implementation of statistical process control methodologies (SPCs) has become an essential and common practice in all pharmaceutical companies in order to achieve a predictable and acceptable level of quality (Mostafa Eissa, 2018; Eissa, 2018a; Essam, 2023). One of the most important SPC tools in the pharmaceutical industry is the Shewhart plot (SPC) (Eissa, 2015). It has a wide range of applications in many industries and non-industries for the assessment and control of processes and inspection parameters (Essam Eissa, 2017; Eissa et al., 2021a, 2021b, 2023a; Eissa, 2023a). Manufacturers of pharmaceutical-grade raw chemicals have expanded all over the world, making it possible to obtain them in retail markets and through brokers anywhere in the world (Eissa, 2023b). However, to ensure the current and future quality of pharmaceutical products, it is essential to ensure sustainable quality assurance for the expected chemical and physical properties.

It is expected that chemical manufacturing facilities are on the rise, especially in developing countries. The quality of chemical manufacturing firms in terms of Good Practices (G×P), including in the pharmaceutical and healthcare sectors, is in dispute (Eissa & Abid, 2018; Eissa, 2018b). The quality of the end product could be a reflection of the quality of the manufacturing process (Kim et al., 2021). Therefore, an organization that has the correct quality concept in place throughout the entire company would produce products that have acceptable, stable, and predictable properties with little chance of failure through effective strategy of SPC application.

In a crisis situation, there is a high likelihood of deterioration of the quality of the goods that are offered by the brokers, the wholesalers and the market retailers to satisfy the needs of the customers with cheap prices at the cost of the necessary quality inspection characteristics. Given the above challenges, the objective of this study was to evaluate the purity and goodness of a chosen excipient that is frequently included in the pharmaceutical preparations of chemical manufacturing companies. This study will focus on a critical test that is officially recognized as one of the essential inspection characteristics of inactive material.

## MATERIAL AND METHODS

A chemical manufacturing plant of raw materials of pharmaceutical grade was assessed for the quality of the manufacturing output [16, 17]. Fifty-five samples of one of the common and classical antihistamine active medicinal materials were investigated for the acidity or alkalinity, related substances, Loss-On-Drying (LOD) and assay result trend (Eissa & Abid, 2018; Eissa, 2023). 2-N, N-dimethylethanamine (diphenylmethoxy) hydrochloride (DPHH) is a sedative and antihistamine that is mostly used to treat allergies, sleeplessness, and cold symptoms. It is also less often used to treat nausea and Parkinsonian tremors (Anonymous, 2020). All tests were done according to the standard method detailed by British Pharmacopoeia (BP) (Eissa, 2023c).

### Official Tests for Acidity or Alkalinity, Related Substances, Loss on Drying and Assay

The British Pharmacopoeia monograph of Diphenhydramine outlines the detailed procedures for testing the active medicinal substance. For acidity and alkalinity, 0.15 mL of methyl red solution R and 0.25 mL of 0.01 M hydrochloric acid are to be added to 10 mL of solution S. The indicator is pink in color, and it takes no more than 0.5 mL of 0.01 M sodium hydroxide to turn it yellow.

For the test solution, 70 mg of the substance under examination is dissolved in the mobile phase and then diluted to a volume of 20.0 mL using the same mobile phase. A further dilution is performed by taking 2.0 mL of this solution and diluting it to 10.0 mL with the mobile phase. The preparation of reference solution (a) involves diluting 1.0 mL of the test solution to 10.0 mL with the mobile phase. This solution is then further diluted by taking 1.0 mL and diluting it to 20.0 mL with the mobile phase. Reference solution (b) is prepared by dissolving 5 mg of diphenhydramine impurity A CRS and 5 mg of diphenylmethanol R in the mobile phase and diluting this to 10.0 mL with the mobile phase. To 2.0 mL of this solution, 1.5 mL of the test solution is added and the resulting solution is diluted to 10.0 mL with the mobile phase.

The column used in this procedure has a length (l) of 0.25 m and a diameter (Ø) of 4.6 mm. The stationary phase is a base-deactivated octylsilyl silica gel for chromatography R (5 µm). The mobile phase is a mixture of 35 volumes of acetonitrile R and 65 volumes of a 5.4 g/L solution of potassium dihydrogen phosphate R, which has been adjusted to a pH of 3.0 using phosphoric acid R. The flow rate is set at 1.2 mL/min. Detection is carried out using a spectrophotometer set at 220 nm. An injection volume of 10 µL is used. The run time is seven times the retention time of diphenhydramine. The relative retention times, with reference to diphenhydramine (retention time = about 6 min), are as follows: impurity A = about 0.9; impurity B = about 1.5; impurity C = about 1.8; impurity D = about 2.6; impurity E = about 5.1. The system suitability is checked using reference solution (b). The resolution should be a minimum of 2.0 between the peaks due to diphenhydramine and impurity A.

The limits are as follows: the correction factor for the calculation of content is 0.7, which is applied to the peak area of impurity D. The area of impurity A should not exceed the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5%). The area of any other impurity should not be more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3%). The total area should not be more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0%). The disregard limit is 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05%).

The loss on drying should not exceed 0.5%, as determined on 1 g by drying in an oven at 105°C. The sulfated ash should not exceed 0.1%, as determined on 1.0 g. For the assay, 0.250 g is dissolved in 50 mL of ethanol (96%) R and 5.0 mL of 0.01 M hydrochloric acid is added. A potentiometric titration is carried out using 0.1 M sodium hydroxide. The volume added between the two points of inflexion is read. 1 mL of 0.1 M sodium hydroxide is equivalent to 29.18 mg of $C_{17}H_{22}ClNO$.

**Statistical Analysis**

To determine the appropriate statistical method for process behavior analysis, data distribution was initially assessed. The Anderson-Darling (AD) test was employed to evaluate the goodness-of-fit of the data to an assumed distribution at a significance level of $\alpha$=0.05. This test measures the discrepancy between the observed data and the expected values under the hypothesized distribution. If the AD test indicated non-conforming data spreading, the Johnson transformation family was applied to transform the data into a more conforming distribution (Eissa, 2023c). This family of transformations includes several distributions capable of accommodating various data shapes.

For data that successfully met the distribution assumption, variable process-behavior charts, including capability analysis, were constructed using Minitab® 17.1.0. However, for datasets that did not conform to any standard distribution, even after transformation, attribute-type (after suitable processing) or Individual (I) control charts were utilized (Eissa, 2023c). In cases where the initial diagnostic U-chart indicated deviations from the assumed Poisson distribution, Laney corrections were applied to adjust for overdispersion or underdispersion. This approach allowed for a comprehensive analysis of the data, selecting the most appropriate statistical method based on the data's characteristics and ensuring accurate interpretation of process behavior.

## RESULTS AND DISCUSSION

This study is a component of an organization-wide assessment aimed at achieving the chemical plant's Total Quality Management (TQM) objectives (Eissa, 2019a; Rashed & Eissa, 2020). Production mistake detection, reduction, and elimination are ongoing processes carried out by the total quality management (TQM) technique (Rashed & Eissa, 2020). It expedites supply chain coordination, guarantees that workers receive the most recent training available, and improves customer satisfaction (Rashed & Eissa, 2020). All parties engaged in the production process must be held responsible for the overall quality of the finished good or service in order to accomplish total quality management. An indispensable analytical technique to achieve this goal is the use of SPC methodologies.

### Box and Whisker Plot (Box Plot)

This diagram showed the dispersion pattern of the datasets and the level of skewness (Eissa, 2022). For Figure 1, it could be noted that various degrees of distortion from the normal pattern were present in the datasets which are less evident in the LOD and assay data. Moreover, the presence of outliers further skewed the results which could be detected in the total impurities and sulfated ash records. In turn, all raw data did not pass the normality tests using the Anderson-Darling (AD) test at P=0.05. Best-fitting distribution identification did not return any valid type of spreading - except for the assay after Johnson transformation to the normal pattern of dispersion – as all P values were < 0.05.

### Checking for Poisson Distribution

While the Poisson assumption is a starting point for many U-chart applications, it's essential to assess the data's distribution to ensure the chart's effectiveness. Data results that could not fit any kind of dispersion – even after transformation, could be adjusted to fit the attribute type of control charts as a number of parts per 10,000 units (depending on the sensitivity of the measurement units). However, checking for the fitness of the presumed Poisson distribution should be verified to avoid misleading control limits with the risk of low or high alarm rates depending on the presence of overdispersion or underdispersion (Eissa, 2019b). Hence, the diagnostic tool of U chart was used as could be seen in Figure 2 for six inspection characteristics. All of them demonstrated the necessity for adopting Laney correction to adjust for data spreading.

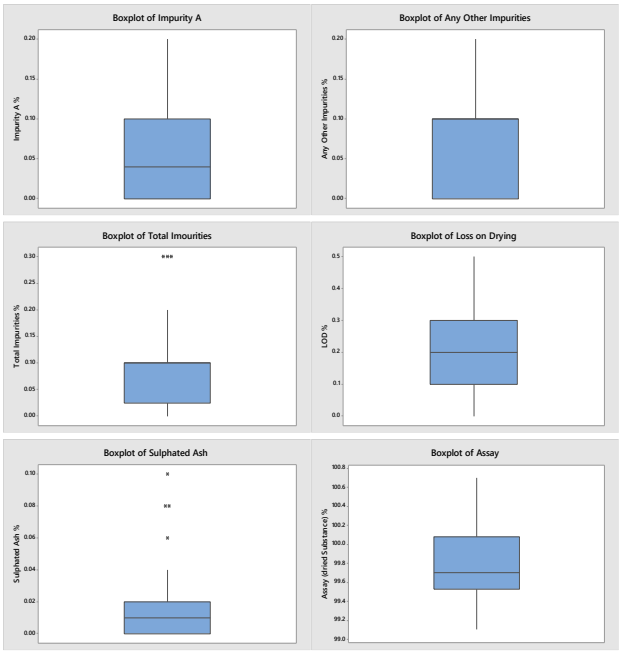


**Figure 1.** Box/Whisker diagram showing the dispersion and skewness of the datasets of the analyzed inspection characteristics via quartiles for one of the first-generation antihistamines of ethanolamine class. Asterisks are indication of the outlier data points

### Laney Process-Behavior and Individual-Moving Range (I-MR) Plots

Many procedures that entail measuring, controlling, and monitoring of the inspection qualities under examination are built around process-behavior charts (Eissa, 2019; 2020b). It is possible to use any of the two Shewhart chart types—variable or attribute control charts—which have been used in the past (Eissa, 2019a, 2023c; Rashed & Eissa, 2020). The different kinds of warnings might be discussed in more depth in other earlier studies (Eissa et al., 2023b). The following guidelines would be used to compute the control window and average that are used in Figures 3 to 6.

Center line (CL) of an individual (I) chart: Mean of the individual data points. For the I chart, the upper

control limit (UCL) is CL + 2.66 x Avg Moving Range. The Lower Control Limit (LCL) for the I chart is equal to CL - 2.66 x Average Moving Range (MR), or 0 in the event that the MR is negative. The center line (CL) of the MR chart represents the mean of MR (Eissa et al., 2023b; Rashed & Eissa, 2020). The Upper Control Limit (UCL) for the MR chart is 3.27 times the Average Moving Range. The Lower Control Limit (LCL) for MR charts is set to zero.

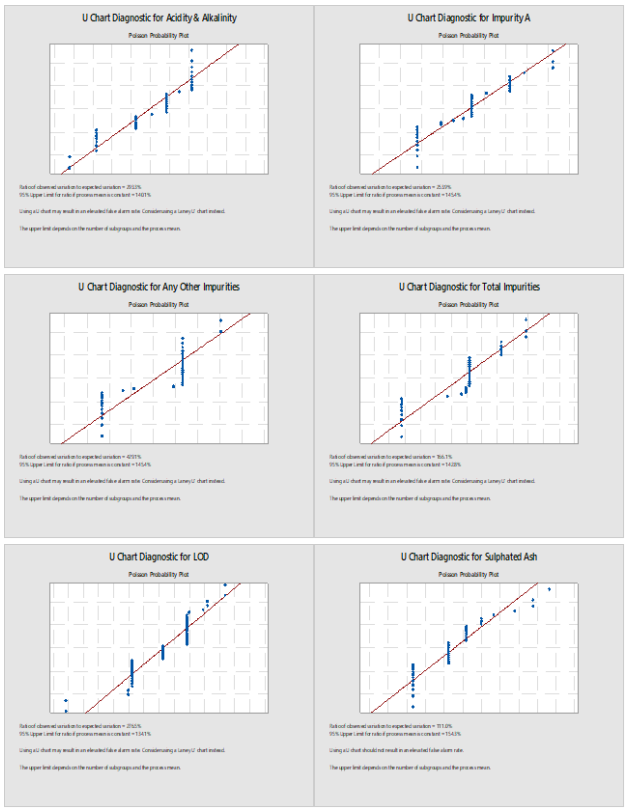


**Figure 2.** Diagnostic U chart for examination of the fitting to the presumed distribution for quality control tests of 2-(diphenylmethoxy)-N,N-dimethylethanamine Hydrochloride

With regard to the U charts, equations 1 through 7 show that the primary components of the trending charts may be calculated for the Laney adjustments. When the data deviates from the Poisson distribution, it might result in inaccurate control limits and subsequent alerts because of overspreading or underdispersion (Eissa, 2017). In such cases, this kind of chart is utilized. In order to use the traditional chart, the ideal dispersion ratio in the U chart diagnosis should be between an acceptable specific range (Eissa et al., 2023). where *ui* is the subgroup's number of defects, *ni* is the subgroup's size, *zi* is the z-score, *u(prime)* is the data mean, and $\sigma z$ is computed as MR(bar)/1.128, where *MR(bar)* is a moving range of length two, the figure is an unbiasing constant, and $\sigma ui$ is the standard deviation. Subgroup i's count rate is ui. The standard deviation that has been adjusted for overdispersion or underspreading is sd(ui).

$$\sigma_{ui} = \sqrt{\bar{u}/n_i} \quad (1)$$

$$z_i = \frac{u_i - \bar{u}}{\sigma_{ui}} \quad (2)$$

$$u_i = \bar{u} + \sigma_{ui}.z_i \quad (3)$$

$$sd(u_i) = \sigma_{ui}.\sigma_z \quad (4)$$

$$CL = \bar{u} \quad (5)$$

$$UCL = \bar{u} + 3.\sigma_{ui}.\sigma_z \quad (6)$$

$$LCL = \bar{u} - 3.\sigma_{ui}.\sigma_z \text{ or } = \text{zero} \quad (7)$$

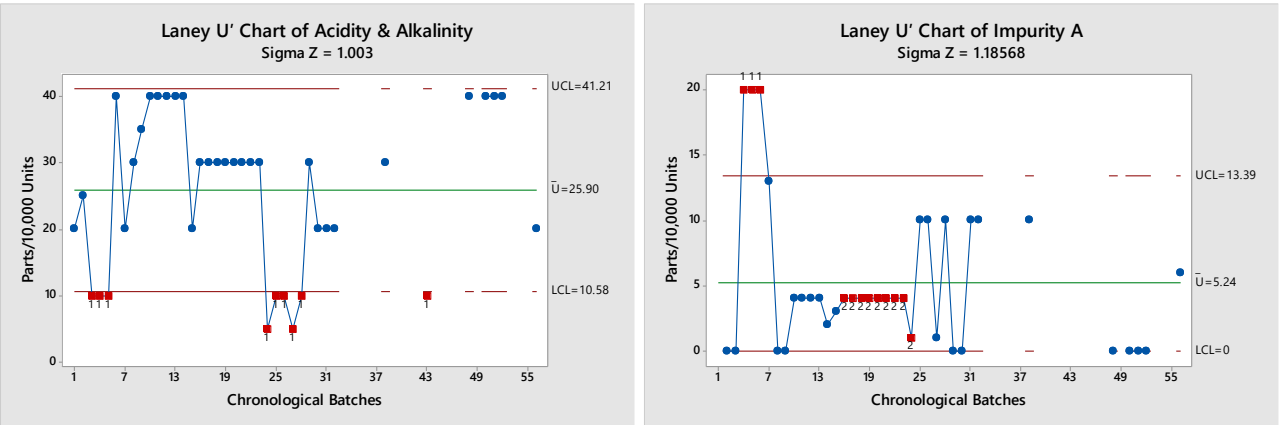


**Figure 3.** Laney-corrected attribute charts for the acidity/alkalinity and impurity A tests

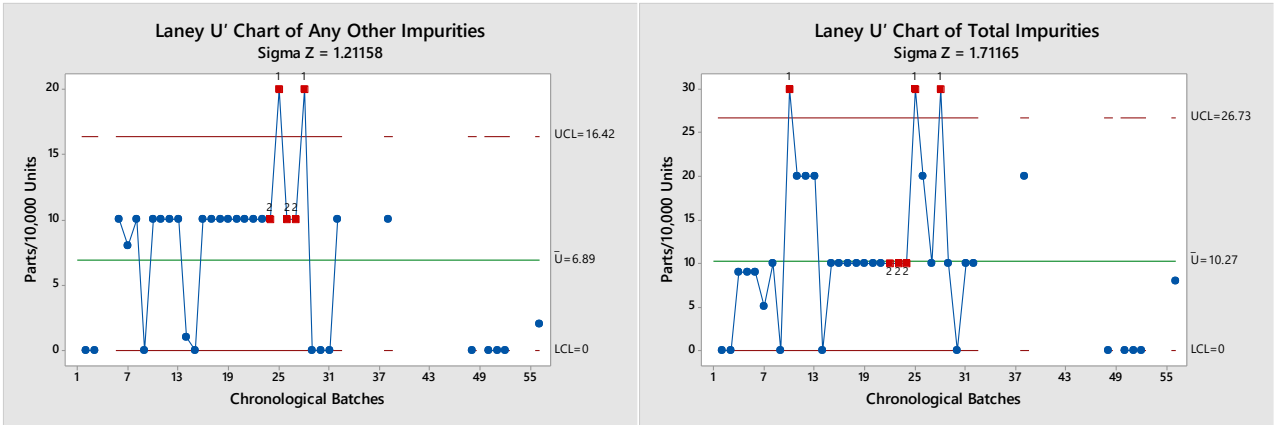


**Figure 4.** Laney-corrected attribute charts for the other impurities and total impurities tests

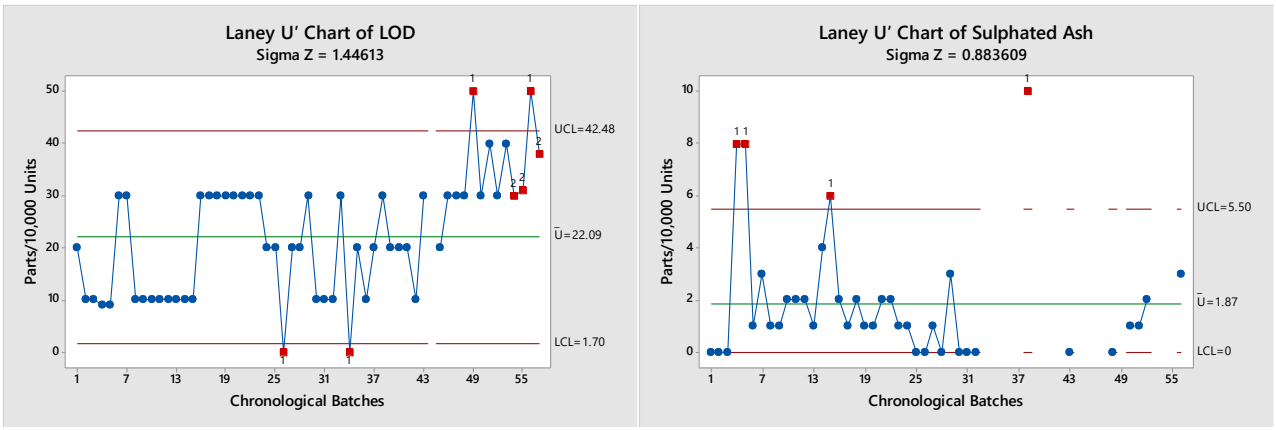


**Figure 5.** Laney-corrected attribute charts for the Loss on Drying (LOD) and sulphated ash tests

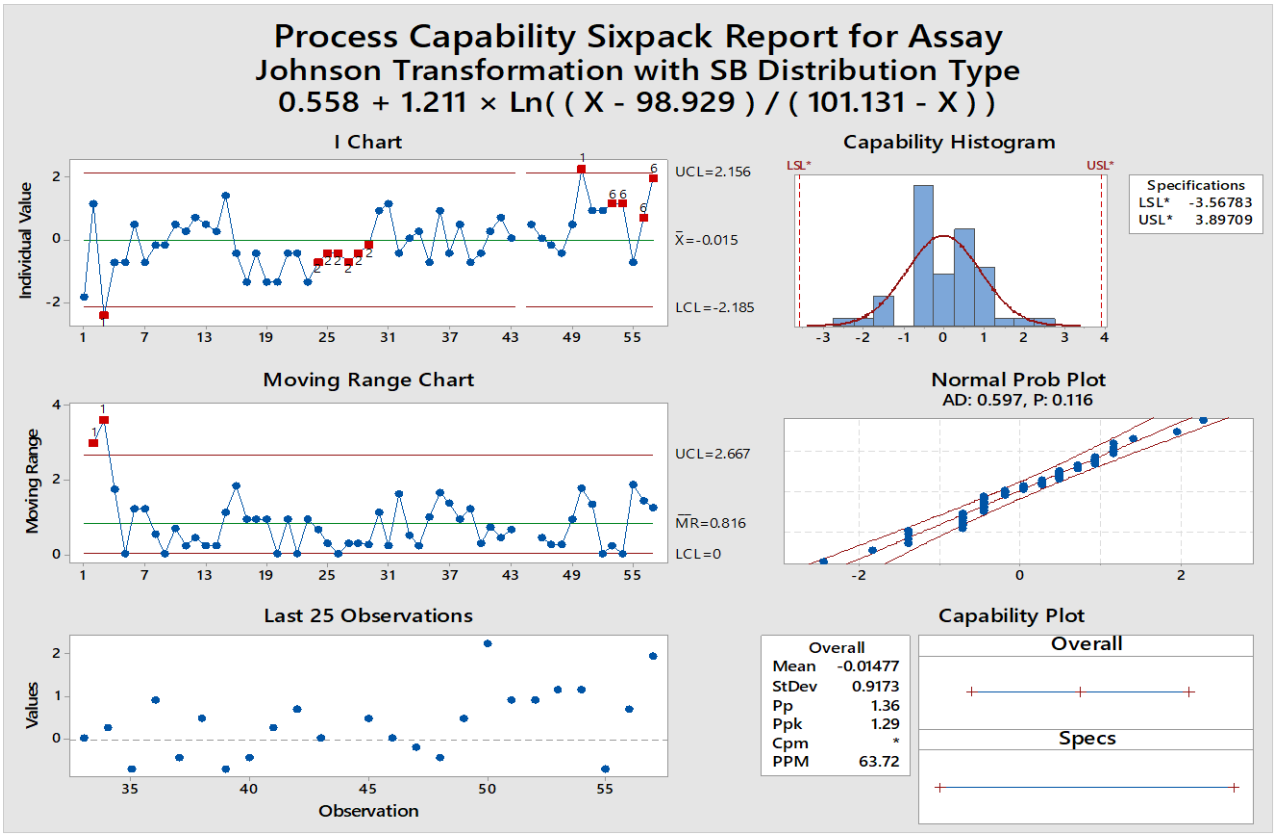


**Figure 6.** Comprehensive overall capability analysis of the assay test based on dried substance using variable trending chart

Based on past experiences, Laney-adjusted control charts have shown to be a useful method for trend analysis of datasets that have not followed certain distribution patterns (van den Ban & Goodwin, 2017). For widely used distributions like Gaussian and Poisson spreading patterns, all inspection criteria failed to show appropriate fitting (Mostafa, 2019). In order to assess the qualities being studied, it was necessary to adjust the data for Laney attribute charts in a way that produced results that could be understood. For the variable control chart of the assay, despite the control limits being confined within the specification range, the presence of several out-of-control points precludes the use of the capability analysis till the stabilization of the process could be accomplished.

Establishing comprehensive SPC methodology implementation is crucial for chemical manufacturing organizations, as it forms an essential component of Total Quality Management (TQM) across the whole enterprise (Ismail, 1998). To enforce safety and quality concepts into the products, however, regulatory monitoring and surveillance in the industrial sector are essential. Until the SPC procedures are properly integrated into the foundations of the legislation governing the chemical sector, the receiver customer should monitor the given lots using appropriate statistical tools to keep a watch on the goods they get (Saha et al., 2022). This is particularly crucial for emerging and economically distressed countries.

The current study identifies a significant and distinctive viewpoint in the physical and chemical criterion-based API trending and monitoring. The highly competitive world of pharmaceutical and medical products demands stringent monitoring and control of the production field's quality (Ahmed Eissa, 2018). The fundamentals, or the raw components, are where this vision starts. Seeing the trending pattern of the inspection properties of the chemical entities is an important task that provides insight into the behavior of the inspection characteristics with the produced batches provided reflecting the condition of the quality delivered to the organization's ultimate clients.

When monitoring a process in a time sequence or serial fashion, control charts are crucial. In order to detect changes in the attributes under examination and ascertain whether these changes are most likely the consequence of common or unique cause variations, limiting thresholds are specified and they display the mean. Statistical analysis and correlation studies would be useful to understand the trending pattern and the properties (chemical and physical) of the manufactured chemical product that is given as a raw material. Ensuring the production of medical supplies that meet consistent, dependable, and satisfactory quality standards is an essential analytical undertaking.

## CONCLUSION

Plots of process behavior derived from datasets that were non-normally distributed as well as the normal assay dataset demonstrated that the produced raw material quality exhibited uncontrollable states as batches progressed in chronological order. In addition, process capability monitoring output cannot be considered until stabilization of the inspection trends could achieved, and in order to enhance the performance index level, there needs to be a tightening of the variances in the inspection characteristic of all tests within the specification's windows. As a result, in order to reduce the possibility of uncontrollable outcomes that exceed the upper and/or lower limiting barrier in the future, the process means should be moved closer to the center. Nevertheless, for one-sided specification, it would be desirable that the trends of the inspection characteristics could be brought toward the diminishing side. It is recommended that pharmaceutical raw materials synthesized by the company should be included in future research investigations together with other inspection qualities of the raw material.

### Compliance with Ethical Standards

### Conflict of Interest

The author declares that there is no conflict of interest.

**Ethical Approval**

The author declares that this document does not require ethics committee approval or any special permission. This study does not cause any harm to the environment.

**Funding**

Not applicable.

**Data Availability**

The data that support the findings of this study are available from the corresponding author on request.

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