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Tracking Stability Using Shewhart Charts to Elucidate Trending Patterns in Glyceryl Guaiacolate Assay: Paving the Way for Quality Improvement in Medicinal Chemical Industry

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ABSTRACT

Shewhart charts are a crucial part of statistical process control, or SPC, which tracks and regulates the pharmaceutical compound's inspection properties. It serves to shed light on the process's present state and, if necessary, the future improvements that will be needed. The trending pattern for the glyceryl guaiacolate assay is the main subject of this investigation. SPC software is used in this work. Following the selection of the most appropriate underlying distribution, Individual-Moving Range (I-MR) charts are used as a trending method for the data. Since some batches in the time series sequence show indications of out-of-control points, improvements are needed to enhance the quality of inspection attributes. Accordingly, capability analysis will not be relied on at this stage till the stabilization of the process. This study highlights the vital role of control charts in ensuring the quality of chemical materials. It contributes to building a robust industrial regulatory system by analyzing the quality of medicinal compounds from chemical manufacturers, especially in developing countries.

INTRODUCTION

There is fierce competition among numerous businesses and corporations in the pharmaceutical and healthcare industries for drugs and medical supplies (Eissa, 2021a). The patient's health comes first, with safety followed by efficacy and quality (Eissa et al., 2016a; Eissa, 2022). Active or inactive medicinal substances ought to serve as the foundation for the standard quality prior to the examination of the inspection qualities of the completed dosage forms.

To reach a high degree of consistent and acceptable quality, statistical process control (SPC) techniques are now widely utilized and deemed vital in all pharmaceutical organizations (Eissa, 2018a). The Shewhart plot is one of the most important SPC tools (Eissa, 2015). It is widely used to evaluate and regulate processes and inspection features in both industrial

and non-industrial domains (Eissa et al., 2021a; Eissa, 2023a; Eissa et al., 2023; Eissa et al., 2021b; Eissa, 2019). The producers of pharmaceutical-grade raw materials have spread across the globe, making them easily accessible to brokers and retail marketplaces everywhere (Eissa & Mahmoud, 2016). However, maintaining consistent quality assurance of the anticipated chemical and physical attributes is crucial to ensuring the pharmaceutical products' worth both now and in the future.

A crisis can lead to a significant drop in the quality of goods accessible from brokers, wholesalers, and market retailers, who may sacrifice important quality inspection features in order to satisfy consumer demand for low costs. Aiming to evaluate the quality and goodness of a particular Active Pharmaceutical Ingredient (API) that is frequently used in pharmaceutical respiratory preparations from chemical manufacturing companies, the current investigation was motivated by the highlighted issues. The investigation will center on a significant test viz. the assay that is formally regarded as one of the essential features for active material inspection.

MATERIAL AND METHODS

Study Subject

A chemical manufacturing facility using pharmaceutical-grade raw materials was evaluated for the quality of its manufactured products (Eissa & Abid, 2018). The assay result trend was examined for more than 120 batches of a common medical substance that is used in cough preparations (Eissa & Mahmoud, 2016; Eissa & Abid, 2018). This expectorant material is (RS)-3-(2-methoxyphenoxy) propane-1,2-($C_{10}H_{14}O_4$). It is ether of glycerin and guaiacol chemically. It can be taken in addition to other prescription drugs for treatment of respiratory conditions.

Analysis of Active Pharmaceutical Compound

The United States Pharmacopeia (USP) standard official procedure – after verification - was used to analyze each manufactured batch with 98.0% to 102.0 % of the anhydrous material is the analytical limit (Eissa & Mahmoud, 2015). HPLC (C18 column) with UV detection (254 nm) would be the assay method. The manufacturing firm executed the assay after performing method validation according to the official compendia.

Results collection and processing

The results of the chemical analysis of the 120 material samples were tabulated in Microsoft Excel Spreadsheet in chronological order after verification of the suitability of the assay test records. Preliminary screening for any error or anomaly was examined before further processing.

Screening for Best Distribution Fitting

The distribution was identified at 95% Confidence Interval (CI) and α 0.05; the Anderson-Darling (AD) test was used to confirm the best-fitting spreading plot. The Johnson family technique was used to normalize raw data that did not follow any clear trend (Eissa, 2023b). If the data passes the normality test, it may then be used for additional analysis. The variable process-behavior charts were drawn using the most appropriate distribution types, together with the corresponding capability plots and capability histograms (Eissa, 2023b). Statistical software was used for all calculations and visualization.

Statistical Process Control of Assay Trend

After distribution identification, the SPC selection will undergo execution following the nature of data spreading using commercial SPC program. Minitab® version 17.1.0 was used to analyze the inspection characteristics in order to check for distribution fitting and create a suitable SPC examination profile (Eissa, 2018b; Eissa e al., 2016b). The control charts, capability assessments, and histograms might be used to determine the initial state of control based on the output findings.

RESULTS AND DISCUSSION

To meet the chemical plant's Total Quality Management (TQM) objectives, the organization is being thoroughly examined, and this project is a part of it (Eissa, 2021b). Reducing, eliminating, or continuously detecting production defects are the goal of total quality management (TQM). Customer satisfaction rises, supply chain coordination is

accelerated, and staffs receive the most recent training available (Eissa, 2021b). Holding all manufacturing process participants accountable for the overall quality of the finished good or service is necessary to attain total quality management.

Figures 1, 2, and 3 present the dataset's detailed dispersion pattern using probability plots. According to the results of the goodness of fit test, only three distributions— the biggest extreme value, Weibull and normal (after Johnson transformation)—are legitimate in that ascending order. The AD, goodness-of-fit figure probability charting and p-values were used to make the selection. This and a related study on the same project line partially agree. The p-value, a probability, evaluates the strength of the evidence refuting the null hypothesis (Rashed & Eissa, 2020). In an AD test, the predicted distribution of the data is the null hypothesis (Eissa, 2021c). Thus, lower p-values provide more evidence that the data deviate from the distribution.

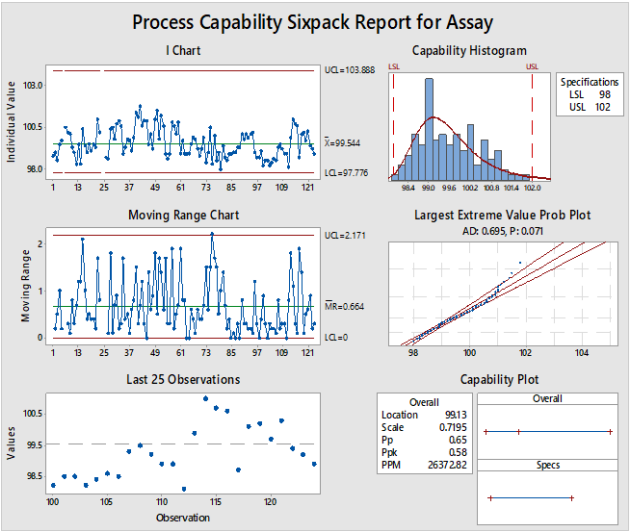

Figure 1. Statistical process inspection of the assay results trend using the largest extreme value distribution assumption

The preliminary examination of Individual-Moving Range (I-MR) process behavior charts in Figures 1, 2 and 3 showed unstable variations – at least at one point - and hence would affect the process means according to the selected types of the best-fitting distributions. Each corresponding dispersion was acceptable according to the probability plot (Eissa & Rashed, 2023). Moreover, the capability histograms illustrated that the spreading of data was not confined within the Lower Specification Limit (LSL) and the Upper Specification Limit (USL).

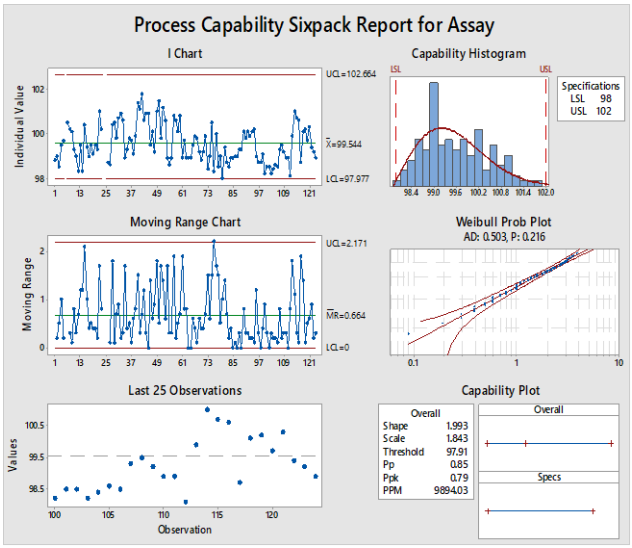

Figure 2. Statistical process inspection of the assay results trend using the Weibull distribution assumption

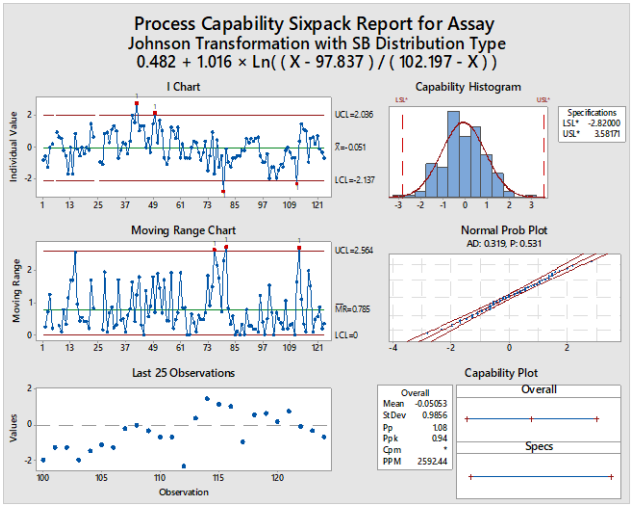

Figure 3. Statistical process inspection of the assay results trend using the normal distribution assumption using Johnson transformation family of SB

Furthermore, the dispersion frequency of the bins approaches the fictitious assumed underlying distribution assumption (Eissa & Hamed, 2019). It is clear from the preliminary findings that the control windows are not centered within the specification's boundaries, increasing the likelihood of an excursion below the lower threshold as well as the upper side, and that the process average is not centered in the middle of the specification window. Based on the previous observations, the current capability analyses

cannot be relied upon until the inspection characteristic can be brought back fully under control through observing the control chart, then reanalyzing the capability plots to verify the state of the process.

It is important to note that in order to guarantee the procurement of raw materials with stable, predictable, and conforming inspection properties indicating a Good Manufacturing Practice (GMP) throughout the production processes, statistical quality monitoring must be established from the outset of the manufacturing process for chemical production. This duty should not be undervalued. When it comes to taking the lead in a competitive market, any respectable business that uses GxP—a typical acronym for quality standards and suggestions that are regarded as "good practice"—must use the system (Eissa & Rashed, 2020). The "x" stands for the various fields in which it might be used. A collection of quality standards is commonly referred to by the acronym GxP. The final dosage forms' functional values would represent the quality of each individual component. In a world where the number of sick people is always rising, this is vital when it comes to the lives and health of the patients.

The above implemented technique could guarantee the monitoring and management of the inspection properties, but transformation might alter the time series plot's original shape, which might make extrapolation during investigation more complex and harder. Additionally, more data—and hence, more batches—are needed to create reliable criteria using control charts in order to restore the inspection characteristic under investigation's quality standards.

CONCLUSION

Based on the non-normally distributed dataset, process-behavior plots were used to illustrate how the manufactured raw material quality fluctuated between batches, exhibiting out-of-control states. Additionally, the process capability monitoring revealed that tightening the differences in the inspection characteristic (assay) between consecutive products is necessary to attain a better performance index level and that performance needs to be improved. The average line is also moved away from the reference center. In order to reduce the possibility of uncontrollable outcomes that are either above or below the limiting thresholds in the future, the process mean should be moved as close to the center as possible. Other medicinal substances made by the manufacturer should be incorporated in future research investigations along with other inspection characteristics of the pharmaceutical raw material. Additionally, as a crucial component of the quality improvement system, the inquiry would include all the chemicals that the pharmaceutical manufacturer produces.

Compliance with Ethical Standards

Conflict of Interest

The author declares that there is no conflict of interest.

Ethical Approval

For this type of study, formal consent is not required.

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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