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Enhancing Process Efficiency in Industry Through Statistical Process Control: Study of Aspartyl Phenylalanine Methyl Ester

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ABSTRACT

Statistical Process Control (SPC) is a critical methodology within the medicinal chemical industry, employed to guarantee the safety, efficacy, and consistency of chemical products. SPC facilitates the identification of deviations from established specifications, thereby minimizing process variability and waste, and ultimately enhancing customer satisfaction. L-aspartyl-L-phenylalanine methyl ester, an artificial sweetener characterized by its low caloric content, represents a manufacturing process that necessitates diligent monitoring and control. Despite its inherent advantages, the implementation of SPC presents certain challenges, including the judicious selection of appropriate data, the accurate interpretation of analytical results, and the seamless integration with existing quality management systems. Data corresponding to selected inspection attributes were imported into Minitab version 17.1.0 for subsequent statistical analysis. Descriptive statistics, encompassing metrics such as mean, standard deviation, skewness, and kurtosis, were calculated for each parameter to provide an initial characterization of the data distribution. The Anderson-Darling test was employed to formally assess the normality of the data distribution. In instances of non-normal data, various transformations, including square root, logarithm, reciprocal, Johnson, and Box-Cox transformations, were explored. The Anderson-Darling test was reapplied to the transformed data to evaluate the effectiveness of these transformations in achieving normality. For data that remained non-normal after initial transformation attempts, the Box-Cox transformation with a lambda (λ) value of 0.5 was applied using Minitab's "Identify Distribution" feature. A comprehensive Process Capability Six-pack Report was subsequently generated for each parameter (specifically, optical rotation, loss on drying, and assay) following the transformation process, utilizing Minitab's "Process Capability Six-pack" functionality. This report comprises six distinct graphical representations and detailed statistical outputs summarizing process performance. Analysis of the optical rotation data indicated a process that, while statistically stable, lacked the necessary capability to consistently meet specifications, suggesting a clear need for process improvement. The study of loss on drying for L-aspartyl-L-phenylalanine 1-methyl ester revealed a process that was neither stable nor capable in the short term, with observed instability and excursions noted in

the control chart components of the report. The assay data, which demonstrated a lognormal distribution, indicated a process that was neither statistically stable nor capable of meeting the required specifications, underscoring the imperative for significant process enhancement. To improve long-term process capability for all parameters, it is essential to identify and systematically eliminate the underlying factors contributing to process variation, coupled with the implementation of continuous monitoring and control strategies. The implementation of reinforced monitoring protocols and the application of continuous process assessment utilizing advanced statistical methodologies can substantially contribute to improved quality assurance outcomes and enhanced process efficiency within the medicinal chemical industry.

INTRODUCTION

Quality control is a vital aspect of the chemical industry, as it ensures the safety, efficacy, and consistency of chemical products (ASQ, 2024). One of the most widely used methods of quality control is statistical process control (SPC), which involves the collection and analysis of data to monitor and improve the performance of a process (Montgomery, 2008). SPC can help detect and prevent deviations from the desired specifications, reduce variability and waste, and enhance customer satisfaction (Montgomery, 2012; ASQ, 2024). However, SPC also poses some challenges and limitations, such as the selection of appropriate data, methods, and tools, the interpretation and communication of results, and the integration of SPC with other quality systems (Bizfluent, 2021). SPC is based on the principle that every process is subject to variation, which can be classified into two types: common cause and special cause (Box & Cox, 1964). Common cause variation is inherent in the process and is due to random factors that are difficult to identify and control (Wheeler, 2000). Special cause variation is not inherent in the process and is due to assignable factors that can be identified and eliminated (Adler et al., 2011).

SPC aims to distinguish between these two types of variation and take appropriate actions accordingly. One of the main tools of SPC is the control chart, which is a graphical display of a process variable over time, with a center line representing the average value and control limits representing the expected range of variation (Oakland, 2003). Control charts can help determine whether a process is in a state of statistical control, meaning that it only exhibits common cause variation, or out of control, meaning that it exhibits special cause variation. Control charts can also help identify trends, cycles, and shifts in the process behavior (Berardinelli, 2013). Another tool of SPC is capability analysis, which is a numerical and graphical evaluation of how well a process meets the customer requirements or specifications (Kane, 1986).

Capability analysis can help measure the performance of a process, compare it with the desired standards, and identify areas for improvement (Eissa & Hamed, 2019). Capability analysis can also help assess the potential of a process, assuming that it is in a state of statistical control, and the actual performance of a process, considering the observed variation (Montgomery, 2013). SPC has been applied to various processes and products in the chemical industry, such as the synthesis, purification, formulation, and packaging of chemicals (Chen et al., 2018). SPC can help ensure the quality and safety of chemical products, such as medicinal and food excipients: N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester (IUPAC name), a low-calorie artificial sweetener used in various food and beverage products (Chemsrc, 2024). N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester is a dipeptide composed of two amino acids, aspartic acid and phenylalanine, and has a complex and sensitive manufacturing process that requires careful monitoring and control (Rozet et al., 2013).

The present study aimed to examine three sets of process capability six-pack reports for L-aspartyl phenylalanine methyl ester, which are comprehensive reports that include six graphs: an individual (I)-chart, a moving range chart, an individual observations plot, a capability histogram with normal curve overlay, a

specialized plot (probability plot), and a capability plot. The reports analyze three quality characteristics of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester: specific optical rotation, loss on drying, and assay. Each report provides information on the stability and capability of the process, such as the mean, the standard deviation, the control limits, the specification limits, the Cp, the Cpk, the Pp, and the Ppk.

MATERIAL AND METHODS

Materials

Data was collected for specific optical rotation, loss on drying, and assay of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester samples from an international chemical manufacturing plant for medicinal compounds based in Asia (Eissa & Mahmoud, 2016; Eissa & Abid, 2018; Eissa, 2016a, 2018a). The raw material specimens were analysed according to the standard official monograph (United States Pharmacopeia, 2023; British Pharmacopoeia Commission, 2024). Minitab® version 17.1.0 commercial software package was used for statistical analysis (Baldassarre et al., 2004; McGraw Hill Education, 2014).

Methods

Distribution Identification

The data was first imported into Minitab version 17 from an Excel file containing the databases. Descriptive statistics were calculated for each parameter (specific optical rotation, loss on drying, and assay) to provide an initial understanding of the data distribution, such as mean, standard deviation, skewness, and kurtosis (Montgomery, 2012). The Anderson-Darling test was employed to check the normality of the data for each parameter. The null hypothesis was that the data follows a normal distribution, and the alternative hypothesis was that the data does not follow a normal distribution (Montgomery, 2013).

A significance level of 0.05 was used for the test. If the p-value was less than 0.05, the null hypothesis was rejected and the data was considered non-normal (Eissa, 2016b). For non-normal data, various transformations were explored to achieve normality, such as square root, logarithm, reciprocal, Johnson and Box-Cox. The transformed data was then tested again for normality using the Anderson-Darling test (Box & Cox, 1964; Montgomery, 2008). The transformation that resulted in the highest p-value and the lowest skewness and kurtosis was selected as the best transformation.

Application of Six-pack for Non-Normal Data

In cases where data remained non-normal after transformation attempts, the Box-Cox transformation with λ=0.5 was applied using Minitab's "Identify Distribution" feature (McGraw Hill Education, 2014). This feature allows the user to compare the data to different distributions and select the best fit based on the p-value, the Anderson-Darling statistic, and the graphical fit (Montgomery, 2013). Process Capability Six-pack Report was generated for each parameter (specific optical rotation, loss on drying, assay) post-transformation using Minitab's "Process Capability Six-pack" feature (McGraw Hill Education, 2014).

This feature allows the user to create a comprehensive report that includes six graphs: an I-chart, a moving range chart, an individual observations plot, a capability histogram with normal curve overlay, a specialized plot (gamma pass plot, Box-Cox transformation plot, or lognormal probability plot), and a capability plot (Wheeler, 2000; Oakland, 2003; Montgomery, 2012). The report provides information on the stability and capability of the process, such as the mean, the standard deviation, the control limits, the specification limits, the Cp, the Cpk, the Pp, and the Ppk (Kane, 1986; Montgomery, 2008). The titles and subtitles of the graphs were customized to include the relevant statistics for each parameter, such as the mean, the standard deviation, the control limits, the specification limits, the Cp, the Cpk, the Pp, and the Ppk (Montgomery, 2012).

RESULTS AND DISCUSSION

Figure 1 shows process capability six-pack reports for N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester (N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester). The reports show the stability and capability of three quality characteristics of N- (L-α-aspartyl)-L-

phenylalanine, 1-methyl ester: specific optical rotation, loss on drying, and assay. Six graphics are included in each report: an individual observations plot, a moving range chart, an I-chart, a capability histogram with normal curve overlay, a specialized plot (gamma pass plot, Box-Cox transformation plot, or lognormal probability plot), and a capability plot. The reports indicate that the process for loss on drying is not stable and capable in the short term, while the processes for specific optical rotation are stable but not capable and assay data are neither stable nor capable.

Specific optical rotation is a measure of how much N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester rotates the plane of polarized light, which indicates its purity and identity (International Council for Harmonisation, 2005; Vaccaro, 2012; United States Pharmacopeia, 2019). The I-chart and the moving range chart show that the process is stable, as the data points are within the control limits (Oakland, 2003; Montgomery, 2013). However, the capability histogram reveals that the data is not normally distributed, as it is skewed, meaning that it is not symmetric around its mean. The gamma pass plot, which compares the data to a gamma dispersion pattern, suggests that the process is not capable, as the data points are outside the specification limits (Oakland, 2003; Montgomery, 2013). This means that the process needs to be improved to meet the acceptance criteria requirements.

Specific optical rotation is an important quality characteristic of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester, as it reflects its molecular structure and composition (United States Pharmacopeia, 2019). A high degree of optical rotation indicates a high purity and identity of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester, which is desirable for its safety and efficacy (International Council for Harmonisation, 2005; Vaccaro, 2012). The process for measuring specific optical rotation should be stable and capable, meaning that it should produce consistent and accurate results that meet the specification limits (Montgomery, 2008). However, the graphs show that the process is not capable, as the data points are outside the specification limits. This implies that some factors affect the optical rotation of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester, such as temperature, pH, solvent, concentration, or impurities. These factors should be identified and controlled by the manufacturer to improve the process capability and ensure the quality of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester.

Loss on drying is a measure of how much moisture is present in N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester, which affects its shelf life and stability (Xiao & Choi, 2002). The I-Chart and the moving range chart indicate that the process is not stable, as some data points are outside the upper control limit (Montgomery, 2012). The distribution identification screening shows that the data is not normally distributed, as it is skewed due to aberrant points of the dataset. However, after applying a Box-Cox transformation with λ=0.5, the data appears to be normally distributed as appeared in the capability histogram and the normal probability plot (Box & Cox, 1964; Montgomery, 2012). The Capability plot, which compares the data with the benchmark reference, indicates that the process is capable and under control, as the data points are within the specification limits for short-term capability (Kane, 1986). This means that the process meets the official specification criteria. This is in contrast to the overall capability.

Another crucial feature of N-(L-α-aspartyl)-L-phenylalanine, 1-methyl ester is its loss during drying, which indicates its stability and moisture content. Low moisture content and good stability of N-(L-α-aspartyl)-L-phenylalanine, 1-methyl ester are indicated by a low degree of loss upon drying, which is advantageous for storage and shelf life. The process for measuring loss on drying should be stable and capable, meaning that it should produce consistent and accurate results that meet the specification limits (Eissa, 2018b). The graphs show that the process is stable and capable for the short term only, as the data points are within the control limits and the specification limits. However, the data is not normally distributed, as it is skewed to the left. This implies that there are some outliers or extreme values that affect the distribution of the data. To overcome this problem, a Box-Cox transformation with λ=0.5 is applied, which transforms the data to a normal distribution (Box & Cox, 1964; Kourti & MacGregor, 1996). This

transformation improves the data analysis and the process capability and ensures the quality monitoring of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester.

Moreover, further interpretation showed that the process for measuring loss on drying for N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester is consistent and accurate in the short term, but not in the long term. This means that the process can meet the specification limits for a small sample of data, but not for a larger sample of data that includes external factors that may affect the process. Some possible reasons for this discrepancy are (Wheeler, 2000; Oakland, 2003; Montgomery, 2008; Eissa et al., 2021, 2023a, 2023b):

- The process is subject to drift or shift over time, which causes the mean or the variation of the process to change (Eissa & Abid, 2018).
- The process is influenced by special causes of variation, such as changes in raw material, equipment, environment, operator, or measurement system.
- The process is not in a state of statistical control, which means that the process output is unpredictable and unstable. To improve the long-term capability of the process, the following steps are recommended:
- Identify and eliminate the sources of variation that affect the process in the long term, using tools such as a cause-and-effect graph (Ishikawa or fishbone diagram) and Pareto chart (Majeske & Hammett, 2003; Montgomery, 2012).
- Monitor and control the process using statistical process control (SPC) techniques, such as control charts, run charts, or process behavior charts (Wheeler, 2000; Oakland, 2003; Montgomery, 2013).
- Perform regular process audits and reviews to ensure the process is maintained and improved over time (Eissa et al., 2021, 2023b).

The assay is a measure of how much N- (L-α-aspartyl)-L-phenylalanine; 1-methyl ester is present in the sample, which reflects its potency and concentration (Chemsrc, 2024). The I-chart and the moving range chart show that the process did not show stable variation at the beginning, as the data points are not all within the control limits (Montgomery, 2008). The lognormal probability plot, which compares the data to a lognormal distribution, indicates that the data is well-fitted by the lognormal spreading (Montgomery, 2012). The capability plot, which compares the data to the lognormal dispersion pattern, indicates that the process is not capable, as the data points are outside the specification limits (Kane, 1986). This means that the process needs to be improved to meet the requirements of the specifications.

The assay is the most important quality characteristic of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester, as it reflects its amount and strength in the sample. A high degree of assay indicates a high amount and strength of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester, which is desirable for its effectiveness and dosage (Chemsrc, 2024). The process for measuring assay should be stable and capable, meaning that it should produce consistent and accurate results that meet the specification limits (Montgomery, 2013). However, the graphs show that the process is not capable, as the data points are outside the specification limits. The data is well-fitted by the lognormal distribution, which is a common distribution for assay data. This distribution reflects the multiplicative nature of assay data, as it is influenced by factors such as dilution, extraction, and calibration (Rozet et al., 2013). However, the lognormal distribution does not guarantee a good process capability, as the data points are still outside the specification limits. This implies that some factors affect the assay of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester, such as degradation, contamination, or measurement error (Chen et al., 2018). These factors should be identified and controlled to improve the process capability and ensure the quality of N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester.

The multiplicative nature of assay data might highlight that the data values are not additive, but rather multiplicative (Box & Draper, 1987; Wright & Royston, 1999; Eissa, 2017). This means that the data

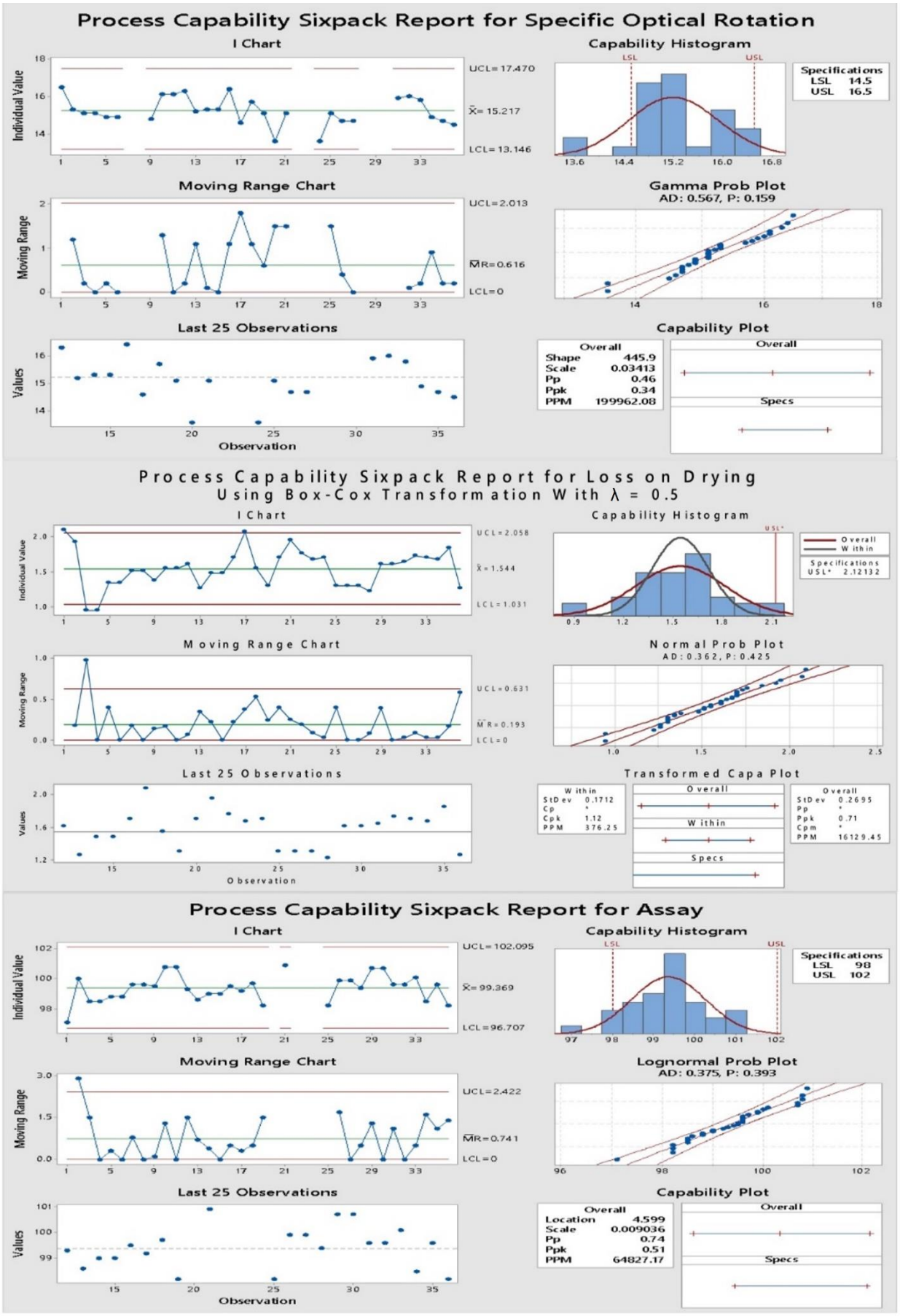

Figure 1. Process Capability Sixpack Reports for N- (L-*α*-aspartyl)-L-phenylalanine, 1-methyl ester (N- (L-*α*-aspartyl)-L-phenylalanine, 1-methyl ester). The reports show the stability and capability of three quality characteristics of N- (L-*α*-aspartyl)-L-phenylalanine, 1-methyl ester

values are influenced by factors that multiply or divide the original value, rather than add or subtract from it (Box & Draper, 1987). For example, if the original value of an assay is 100, and the factor is 0.9, then the resulting value is 90, which is obtained by multiplying 100 by 0.9 (Wright & Royston, 1999). Similarly, if the factor is 1.1, then the resulting value is 110, which is obtained by multiplying 100 by 1.1. This is different from additive data, where the resulting value is obtained by adding or subtracting a constant from the original value (Eissa, 2016b, 2017). For example, if the original value is 100, and the constant is 10, then the resulting value is either 90 or 110, depending on whether the constant is subtracted or added. In biological and chemical assays, when the data values are influenced by variables like dilution, extraction, and calibration, the multiplicative character of assay data is frequently observed. These factors can change the concentration or potency of the analyte, which is the substance being measured by the assay. The lognormal distribution is a common distribution for multiplicative data, as it can model the variability and skewness of the data (Box & Draper, 1987; Wright & Royston, 1999; Eissa, 2017). The lognormal distribution is defined by the logarithm of the data values, which are normally distributed. Therefore, to analyze multiplicative data, it is often necessary to transform the data by taking the logarithm, which converts the data to additive data. This transformation can improve the data analysis and the process capability, as it can reduce the skewness and the variability of the data (Box & Draper, 1987; Wright & Royston, 1999; Eissa et al., 2016; Eissa, 2017).

CONCLUSION

SPC has many benefits for the chemical industry, such as: (i) improving the quality and consistency of chemical products by detecting and preventing deviations from the specifications, (ii) reducing the costs and risks associated with rework, scrap, waste, defects, recalls, and customer complaints, (iii) enhancing the efficiency and productivity of the processes by optimizing the operating conditions and reducing the variability and downtime, (iv) increasing the customer satisfaction and loyalty by meeting or exceeding their expectations and requirements. However, SPC has some challenges and limitations, such as: (i) selecting the appropriate data, methods, and tools for the specific process and product, considering the type, size, frequency, distribution, and transformation of the data, (ii) interpreting and communicating the results of the SPC analysis, considering the statistical significance, practical relevance, and uncertainty of the findings, (iii) integrating SPC with other quality systems, such as quality by design, quality risk management, and quality assurance, to achieve a holistic and systematic approach to quality management.

The previous analysis showed that the consistency of the raw chemical quality is not adequate and further improvements for the quality of the initial batches are needed through customization and optimization of the key manufacturing procedures. These insights are crucial in ensuring quality control and consistency in N- (L-α-aspartyl)-L-phenylalanine, 1-methyl ester production. As future perspective, enhancing monitoring protocols to optimize specific optical rotation, loss-on-drying and assay processes can lead to improved quality assurance. Continuous assessment using advanced statistical tools will be pivotal in achieving enhanced process efficiency.

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.

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Not applicable.

Data Availability

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

AI Disclosure

The author confirms that no generative AI was used in writing this manuscript or creating images, tables, or graphics.

REFERENCES

Adler, Y., Shper, V., & Maksimova, O. (2011). Assignable causes of variation and statistical models: Another approach to an old topic. *Quality and Reliability Engineering International*, *27*(5), 623-628. https://doi.org/10.1002/qre.1168

ASQ. (2024). *What is statistical process control? SPC quality tools*. American Society for Quality (ASQ). Retrieved on May 30, 2024, from https://asq.org/quality-resources/statistical-process-control?srsltid=AfmBOooBmOFvZHSBu6m5jwAG8wAU_lVdde_F_joVw6WBYnu8PmecOcyY

Baldassarre, T., Boffoli, N., Caivano, D., & Visaggio, G. (2004). Managing software process improvement (SPI) through statistical process control (SPC). In F. Bomarius, & H. Iida (Eds.), *Product Focused Software Process Improvement. PROFES 2004. Lecture Notes in Computer Science, vol 3009*. Springer. https://doi.org/10.1007/978-3-540-24659-6_3

Berardinelli, C. (2013, March 7). *A guide to control charts*. iSixSigma. Retrieved on May 30, 2024, from https://www.isixsigma.com/control-charts/a-guide-to-control-charts/

Bizfluent. (2021, January 25). *What are the disadvantages of SPC?* Retrieved on May 30, 2024, from https://bizfluent.com/info-12044671-disadvantages-spc.html

Box, G. E. P., & Cox, D. R. (1964). An analysis of transformations. *Journal of the Royal Statistical Society. Series B (Methodological)*, *26*(2), 211-252. https://doi.org/10.1111/j.2517-6161.1964.tb00553.x

Box, G. E. P., & Draper, N. R. (1987). *Empirical model-building and response surfaces*. John Wiley and Sons.

British Pharmacopoeia Commission. (2024). *British pharmacopoeia* (2024 ed.). The Stationery Office.

Chemsrc. (2024). Aspartame | CAS#:22839-47-0. Retrieved on January 11, 2024, from https://www.chemsrc.com/en/cas/22839-47-0_15039.html

Chen, Y., Wang, J., Zhang, Y., & Li, Z. (2018). Statistical process control for quality improvement of aspartame production. *Journal of Cleaner Production*, *172*, 2840-2848. https://doi.org/10.1016/j.jclepro.2017.11.088

Eissa, M. E. (2016a). Microbiological assessment of compressed air at a pharmaceutical industry: statistical process control. *Journal of Applied Pharmaceutical Sciences*, *3*(1), 23-28.

Eissa, M. E. (2016b). Shewhart control chart in microbiological quality control of purified water and its use in quantitative risk evaluation. *Pharmaceutical and Biosciences Journal*, *4*(1), 45-51. https://doi.org/10.20510/ukjpb/4/i1/87845

Eissa, M. E. (2017). Application of control charts in quality characteristics evaluation of microbiological media. *Journal of Advanced Research in Pharmaceutical Sciences and Pharmacology Interventions*, *1*(1), 1-13.

Eissa, M. E. (2018a). Role of statistical process control of pharmaceutical product to monitor consistency of the manufacturing operation. *EC Pharmacology and Toxicology*, *6*(6), 439-444.

Eissa, M. E. (2018b). Variable and attribute control charts in trend analysis of active pharmaceutical components: Process efficiency monitoring and comparative study. *Experimental Medicine*, *1*(1), 31-44.

Eissa, M. E., & Abid, A. M. (2018). Application of statistical process control for spotting compliance to good pharmaceutical practice. *Brazilian Journal of Pharmaceutical Sciences*, *54*(2), e17499. https://doi.org/10.1590/s2175-97902018000217499

Eissa, M. E., & Hamed, H. S. (2019). Application of statistical quality control tools for monitoring of pharmaceutical product properties: SISPQ, GxP, pharmaceutical product, drug properties. *Pakistan Journal of Scientific and Industrial Research Series B: Biological Sciences*, *62*(1), 39-48. https://doi.org/10.52763/PJSIR.BIOL.SCI.62.1.2019.39.48

Eissa, M. E., & Mahmoud, A. (2016). Evaluation of microbial recovery from raw materials for pharmaceutical use. *Journal of Food and Pharmaceutical Sciences*, *4*(1), 6-11.

Eissa, M. E., Mahmoud, A. M., & Nouby, A. S. (2016). Statistical process control in the evaluation of microbiological surface cleanliness quality and spotting the defects in clean area of pharmaceutical manufacturing facility. *Haya: The Saudi Journal of Life Sciences*, *1*(1), 17-24.

Eissa, M., Rashed, E., & Eissa, D. E. (2021). Quality improvement in routine inspection and control of healthcare products using statistical intervention of long-term data trend. *Dicle Üniversitesi Fen Bilimleri Enstitüsü Dergisi*, *10*(2), 163-184.

Eissa, M., Rashed, E., & Eissa, D. E. (2023b). Microbiological stability assessment of municipal distribution line using control chart approach for total bioburden count. *Health Academy Kastamonu*, *8*(2), 363-383. https://doi.org/10.25279/sak.1035879

Essam Eissa, M., Rashed, E. R., & Eissa, D. E. (2023). Case of preferential selection of attribute over variable control charts in trend analysis of microbiological count in water. *Acta Natura et Scientia*, *4*(1), 1-9. https://doi.org/10.29329/actanatsci.2023.353.01

International Council for Harmonisation (ICH). (2005). *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Pharmaceutical Development Q8(R2)*. Retrieved on May 30, 2024, from https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf

Kane, V. E. (1986). Process capability indices. *Journal of Quality Technology*, *18*(1), 41-52. https://doi.org/10.1080/00224065.1986.11978984

Kourti, T., & MacGregor, J. F. (1996). Multivariate SPC methods for process and product monitoring. *Journal of Quality Technology*, *28*(4), 409-428. https://doi.org/10.1080/00224065.1996.11979699

Majeske, K. D., & Hammett, P. C. (2003). Identifying sources of variation in sheet metal stamping. *International Journal of Flexible Manufacturing Systems*, *15*(1), 5-18. https://doi.org/10.1023/A:1023993806025

McGraw Hill Education. (2014). *Minitab 14 manual*. Retrieved on May 30, 2024, from https://glencoe.mheducation.com/sites/0010126585/student_view0/minitab_14_manual.html

Montgomery, D. C. (2008). *Introduction to statistical quality control* (6th ed.). John Wiley and Sons.

Montgomery, D. C. (2012). *Introduction to statistical quality control* (7th ed.). John Wiley and Sons.

Montgomery, D. C. (2013). *Statistical process control* (7th ed.). John Wiley and Sons.

Oakland, J. S. (2003). *Statistical process control* (6th ed.). Butterworth-Heinemann.

Rozet, E., Lebrun, P., Hubert, P., Debrus, B., & Boulanger, B. (2013). Design Spaces for analytical methods. *TrAC Trends in Analytical Chemistry*, *102*(3), 157-167. https://doi.org/10.1016/j.trac.2012.09.007

United States Pharmacopeia. (2019). *General Chapter <781> Optical Rotation*. Retrieved on May 30, 2024, from https://www.usp.org/compounding/general-chapter-781-optical-rotation

United States Pharmacopeia. (2023). *The national formulary (USP 46-NF 41).* United States Pharmacopeial Convention.

Vaccaro, P. H. (2012). Optical rotation and intrinsic optical activity. In N. Berova, P. L. Polavarapu, K. Nakanishi & R. W. Woody (Eds.), *Comprehensive Chiroptical Spectroscopy: Instrumentation, Methodologies, and Theoretical Simulations, Volume 1* (pp. 275-323). John Wiley & Sons, Inc. https://doi.org/10.1002/9781118120187.ch11

Wheeler, D. J. (2000). *Understanding variation: The key to managing chaos* (2nd ed.). SPC Press.

Wright, E. M., & Royston, P. (1999). Calculating reference intervals for laboratory measurements. *Statistical Methods in Medical Research*, *8*(2), 93-112. https://doi.org/10.1177/096228029900800202

Xiao, D., & Choi, M. M. (2002). Aspartame optical biosensor with bienzyme-immobilized eggshell membrane and oxygen-sensitive optode membrane. *Analytical Chemistry*, *74*(4), 863-870. https://doi.org/10.1021/ac001097a