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Assessment of Some Inspection Properties of Commonly Used Medicinal Excipients Using Statistical Process Control for Monitoring of Manufacturer Quality

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ABSTRACT

This study is a component of a larger initiative that involves the assessment and screening of pharmaceutical and chemical factories that produce medical substances, particularly in Asia and export them to poor nations. The present study concentrated on the inactive pharmaceutical ingredients of a frequently used excipient in pharmaceutical products made of amylopectin and amylose, named Amylum Maydis by the International Union of Pure and Applied Chemistry (IUPAC) nomenclature. This compound has the chemical formula $C_6H_{10}O_5$. Manufacturers asserted that all raw ingredients complied with the British Pharmacopoeia (BP), harmonizing requirements and analytical criteria in the process. As a result, every test complied with the official standard procedures described in the raw material testing monograph. The chosen tests included oxidizing agents, sulfated ash, and loss on drying (LOD). Software for statistical process control, or SPC, was used to collect and handle datasets. Preliminary data examination was done using box plots and three variable visualization techniques associated with the correlation matrix. All results showed that improvements of the inspection characteristics records are mandated to show stable variations even if there was no out-of-specification detected. Accordingly, the output of the tests should be investigated to correct for the assignable causes of the variations. It should be noted that the present data did not follow specific distributions, especially with the presence of aberrant values. Furthermore, it was found that there were several out-of-control points even in cases where there was no deviation from the specification, highlighting the need for suitable inquiry and correction for assignable reasons of variances among batches. Government enforcement of industrial SPC regulations is necessary to ensure the safety and quality of produced medical substances.

INTRODUCTION

As pharmaceutical manufacturing moves towards continuous processing with Process Analytical Technology (PAT) tools, it is important to have effective monitoring and control strategies to ensure consistent and high quality of pharmaceutical products (Wierzbicki et al., 2022). Statistical process control (SPC) can be a useful tool for monitoring critical quality attributes (CQAs) and facilitating continuous process verification (Hahn et al., 2023; Sharma et al., 2024). Commonly used pharmaceutical excipients play an important role in determining the quality and performance properties of drug products (You et al., 2022). As such, it is necessary to assess key inspection properties of excipients and ensure they meet manufacturer specifications using appropriate quality control methods such as SPC. This will help in the monitoring of excipient quality and manufacturer performance over time **(**Kim & Choi 2020; Kim et al., 2021**)**. Together, the implementation of PAT and SPC can enable real-time release and reliable continuous monitoring of unit operations as well as excipient quality.

To attain a consistent and acceptable level of quality, the use of statistical process control techniques (SPCs) has become a standard procedure in pharmaceutical firms (Eissa et al., 2016; Mostafa-Eissa, 2018; Eissa, 2021). The Shewhart plot (SPC) is one of the most crucial SPC instruments in the medicinal and healthcare sector (Eissa, 2015). It has a broad variety of applications for process and inspection parameter evaluation and control in several industries and non-industries (Essam-Eissa, 2017; Eissa et al., 2021a, 2021b, 2023; Eissa, 2023a). Pharmaceutical-grade raw chemical manufacturers have spread throughout the globe, enabling its availability through supply chain system and retail marketplaces worldwide (Eissa & Rashed, 2020). However, sustainable quality assurance for the anticipated chemical and physical qualities is crucial to guaranteeing the quality of pharmaceutical goods both now and in the future.

It is anticipated that there will be an increase in chemical production facilities, particularly in economically emerging nations. There is disagreement over how well chemical manufacturing companies adhere to Good Practices (G×P), particularly in the pharmaceutical and healthcare industries (Eissa, 2018; Eissa & Abid, 2018). The caliber of the production process may be reflected in the final product's quality (Eissa, 2016). Therefore, with an efficient strategy of SPC application, an organization with the right quality concept in place throughout the entire firm would generate goods with acceptable, stable, and predictable qualities with a low likelihood of failure.

In an era of severe global economic conditions, there is a good chance that the quality of the goods supplied by manufacturers, suppliers, and market retailers will decline in order to meet consumer demands for low prices at the expense of essential quality control features. In light of the aforementioned difficulties, the goal of this investigation was to assess the quality and purity of a selected excipient that is commonly used in pharmaceutical preparations by chemical manufacturing firms. This investigation will center on a crucial examination that is formally acknowledged as one of the fundamental features of inactive material inspection.

MATERIAL AND METHODS

Subject of the Study and the Tests

The quality of the manufacturing output from a chemical manufacturing facility using pharmaceutical and medical-grade raw materials was evaluated (Eissa & Mahmoud, 2016; Eissa, 2022). Loss-on-drying (LOD), residue on ignition result trend, and oxidizing chemicals were examined in 41 samples of a common and traditional inactive medicinal excipient (Eissa & Mahmoud, 2016; Eissa, 2022). The starch known as Amylum Mayd, which contains amylopectin and amylose, is frequently used to make oral solid dosage forms, including bulk granules, tablets, and capsules, as well as medicinal and cosmetic powders. Conventional dosage forms such as lubricants, diluents, glidants, and binders all use native starch. Every test was conducted following the British Pharmacopoeia (BP) standard procedure (BP, 2023; Maize Starch, 2023).

Statistical Analysis

To ensure data normality for statistical analysis, the Anderson-Darling (AD) test was employed at a 95% confidence interval (CI) and α = 0.05. This step verifies if the data follows a normal distribution, a common assumption for many statistical tests. If the data deviated from normality after attempting normalization techniques like the Johnson family, Box-Cox, or logarithmic transformations, Shewhart control charts with corrections for overdispersion or under dispersion were used to monitor trends (Eissa, 2019; Mostafa-Essam, 2019; Eissa, 2023b). In addition, the data were subjected to additional analysis through box plot visualization to interpret the dispersion pattern, mean, median and the presence of outliers. Process-behavior charts were examined for the out-of-control signs and accordingly, a decision for further search into capability analyses would be determined. Version 17.1.0 of Minitab®, an SPC program, was used for all computations. Adjusting the findings to the appropriate trending charts was done when no particular spreading pattern appeared appropriate for the datasets (Essam-Eissa & Refaat-Rashed, 2021). GraphPad Prism version 6.01 was used for the descriptive statistics, correlation matrix analysis and comprehensive normality tests at α 0.05. SPC software was also used for the preliminary assessment of the three variables under study using a contour plot and bubble graph (Eissa, 2018; Eissa et al., 2021b). The correlation matrix is used for the following: Identifying potential relationships between inspection aspects, assessing the strength and direction of relationships and guiding further investigation and process improvement, in addition to informing future studies.

RESULTS AND DISCUSSION

The goal of the organization-wide evaluation, which includes this research, is to meet the Total Quality Management (TQM) goals of the chemical plant (Eissa, 2023b). The process of identifying, minimizing and getting rid of production errors is something that the total quality management (TQM) approach does continuously (Al-Najjar, 1996). It increases customer satisfaction, ensures the competence of the workers or the manpower and speeds up supply chain coordination (Rashid & Haris Aslam, 2012). To achieve complete quality management, every person involved in the manufacturing process must be held accountable for the overall Caliber of the final product or service. Using SPC approaches is a crucial analytical strategy to accomplish this aim. This study serves the basis as one part of holistic survey research in collaboration with the official governmental industrial agencies to control and monitor the standards of the chemical manufacturing industries.

Inspection Aspects Association, Characteristics and Visualization

The association between the three variables under investigation can be seen in Figure 1. The investigation of the correlation between the quality control aspects is detailed in Table 1 using the non-parametric Spearman or ϱ (rho) test which complements the previous graph. It could be summarized that there was no specific association between the examined characteristics after 41 points. The correlation ranged from very weak to weak. The p-value is the probability that random sampling would produce a correlation coefficient as close to zero as possible in this experiment if there is no connection between the two variables generally (Rice, 1989). Incorporating a correlation matrix would offer a more comprehensive understanding of the relationships between the investigated quality control aspects, potentially leading to improved process control and future research directions.

The study examines three quality control aspects: loss-on-drying (LOD), residue on ignition, and oxidizing substances. While the Spearman correlation coefficient is used to assess individual relationships between these aspects, a correlation matrix allows for a comprehensive overview of all pairwise correlations simultaneously. This can reveal hidden patterns or unexpected relationships that might not be evident from individual tests. The correlation coefficient calculated for each pair of variables indicates the strength and direction of the relationship. A positive coefficient suggests a tendency for both aspects to increase or decrease together, while a negative

coefficient suggests an opposite tendency. The magnitude of the coefficient (closer to 1 or -1) signifies a stronger relationship. By identifying potentially correlated aspects, the study can prioritize further investigation into the underlying reasons behind these relationships. This knowledge can be crucial for optimizing the manufacturing process to achieve better control over multiple quality characteristics simultaneously. Understanding the relationships between these aspects can inform the design of future studies. By focusing on aspects with strong correlations, researchers can gain a deeper understanding of how changes in one aspect might impact the others, leading to more efficient and targeted investigations.

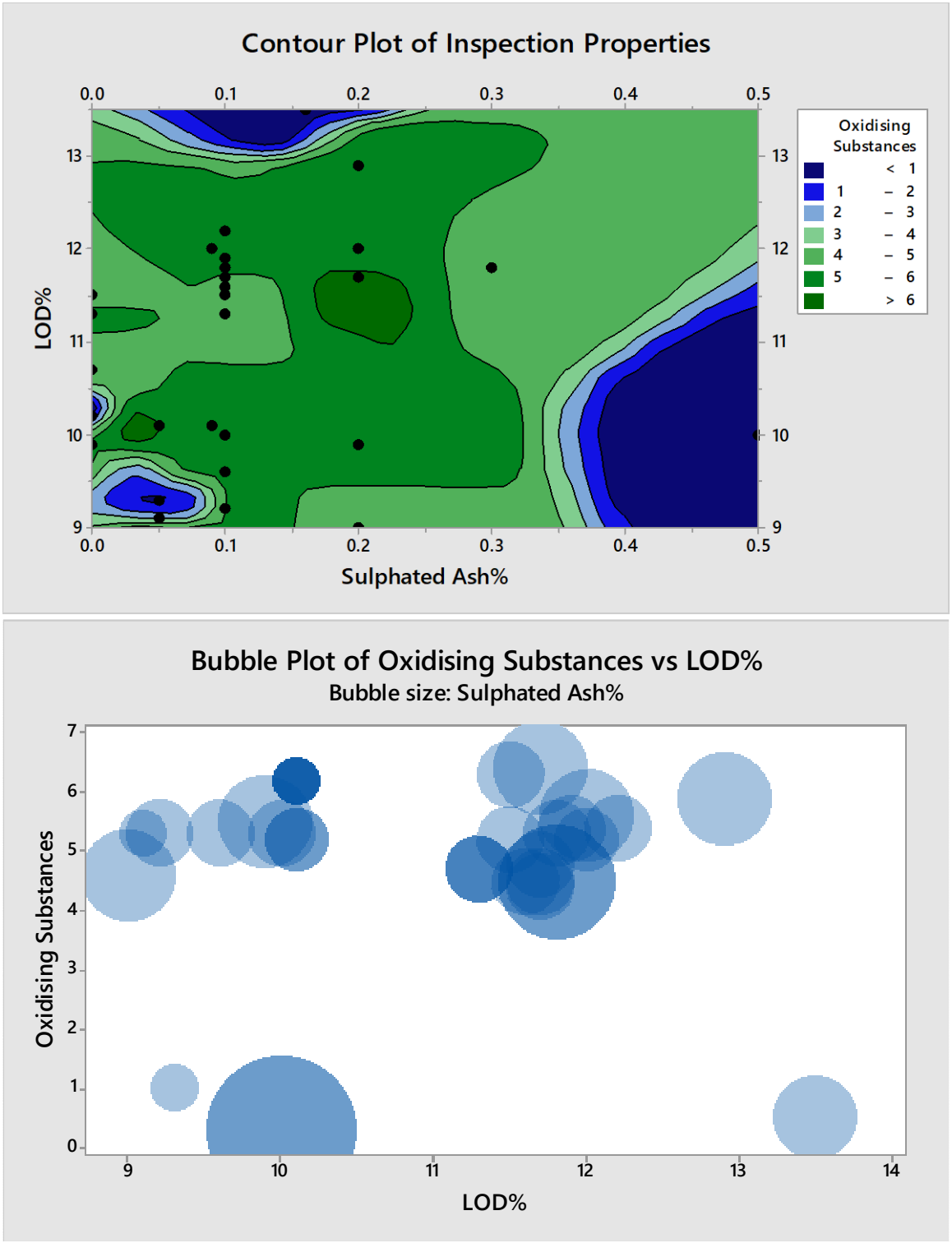

Figure 1. Visualization plots for three variables using contour graph (upper) and bubble chart (lower)

Table 1. Spearman correlation (ϱ) matrix showing (r) and (p) data with criteria range

Oxidizing Substances	**Loss on Drying**	**Sulphated Ash**	**Inspection Characteristics (r)**		
	-0.02	-0.15	**Oxidizing Substances**		
-0.02		0.28	**Loss on Drying**		
-0.15	0.28		**Sulphated Ash**		
Correlation coefficient (r)		Lower	Upper	Lower	Upper
Very weak		0.00	0.19	0.00	-0.19
Weak		0.20	0.39	-0.20	-0.39
Moderate		0.40	0.59	-0.40	-0.59
Strong		0.60	0.79	**-0.60**	**-0.79**
Very Strong		0.80	1.00	-0.80	-1.00
Oxidizing Substances	**Loss on Drying**	**Sulphated Ash**			
	89.7%	35.9%	**Oxidizing Substances**		
89.7%		7.8%	**Loss on Drying**		
35.9%	7.8%		**Sulphated Ash**		
P-value	**P-value %**		**Evidence for rejecting H_0**		
More than 0.1	>	10%	Very weak to none		
Between 0.1 - 0.05	5%	10%	Weak		
Between 0.05 - 0.01	5%	1%	Strong		
Less than 0.01	<	1%	Very strong		

Note: Oxidizing substances, loss on drying and sulphated ash are the tested inspection characteristics of corn flour of medicinal grade.

The coefficient of variations (as a percentage) for oxidizing substances, LOD and sulfated ash was 36.34%, 9.98% and 93.64%, with a total sum of each was 192.4, 445.7 and 4.930, respectively. Results were generated according to the computation done by the statistical software (Motulsky, 2007). D'Agostino and Pearson omnibus, Shapiro-Wilk (SW) and Kolmogorov-Smirnov (KS) normality tests normality test with K2, W and KS statistics, P value, passage of normality test (α=0.05) and P-value summary for oxidizing substances were 21.64, < 0.0001, No, ****, 0.7167, < 0.0001, No, ****, 0.3102, < 0.0001, No, ****, -1.833 and 2.532, LOD were 1.442, 0.4863, Yes, not significant (ns), 0.9327, 0.0177, No, *, 0.2002, 0.0003, No, ***, 0.1753 and -0.6760 and sulphated ash were 29.39, < 0.0001, No, ****, 0.7557, < 0.0001, No, ****, 0.3274, < 0.0001, No, ****, 2.064 and 4.919, respectively. Several tests were shown together for addressing the strengths and weaknesses of each test and to examine potential conflicts of results.

The use of non-parametric statistical tests was sought more convenient for the following reasons:

***Non-normal data distribution*:** The normality tests revealed the data for all three quality control aspects (oxidizing substances, LOD, and sulfated ash) were not normally distributed. The p-values from the normality tests were all less than 0.05, indicating a rejection of the null hypothesis that the data follow a normal distribution.

Rank-based method: The Spearman test is a rank-based correlation test, meaning it analyzes the order or ranking of the data points rather than their actual values. This makes it more reliable than the commonly used Pearson correlation coefficient when dealing with non-normal data. The Pearson correlation coefficient assumes normality and can be misleading if the data is not normally distributed. Therefore, the Spearman test was chosen as a more appropriate statistical method for analyzing the relationship between the quality control aspects due to the non-normality of the data. It utilizes the ranking of the data

points, making it robust against the influence of extreme values or non-normal distributions.

Box and Whisker Plot (Box Plot)

Figure 2 displayed the degree of skewness and the data sets' dispersion pattern (Besseris, 2013). Regarding Figure 2, it can be observed that the datasets exhibited varying degrees of distortion from the regular pattern, which are not as noticeable in the LOD. Additionally, the results of the oxidizing substances and sulfated ash records were further skewed by the existence of outliers. Consequently, the AD test at P = 0.05 was used to test for normality, and all raw data failed. Even after all forms of changes, best-fitting distribution identification could not yield any meaningful spreading since all P values were less than 0.05 with a 95% confidence interval. The AD test is another commonly used statistical test to assess normality, and it was employed here to confirm the previous tests' conclusions and support findings. The AD test confirmed that the data for all three quality control aspects were not normally distributed ($p < 0.05$).

The descriptive statistics of the distribution of datasets as minimum, 25% percentile, median, 75% percentile, maximum, 10% percentile, 90% percentile, mean, standard deviation, standard error of mean, lower 95% CI of mean, upper 95% CI of mean, lower 95% CI of median and upper 95% CI of median (Chang et al., 2019). For oxidizing substances, LOD and sulphated ash, the results were (0.2500, 4.500, 5.200, 5.550, 6.400, 0.6000, 6.200, 4.691, 1.705, 0.2663, 4.153, 5.230, 4.700 and 5.300), (9.000, 10.05, 11.30, 11.70, 13.50, 9.360, 12.00, 10.87, 1.085, 0.1695, 10.53, 11.21,10.10 and 11.60), (0.0, 0.0500, 0.1000, 0.1300, 0.5000, 0.0, 0.2800, 0.1202, 0.1126, 0.01758, 0.08470, 0.1558, 0.0900 and 0.1000), respectively (Table 2).

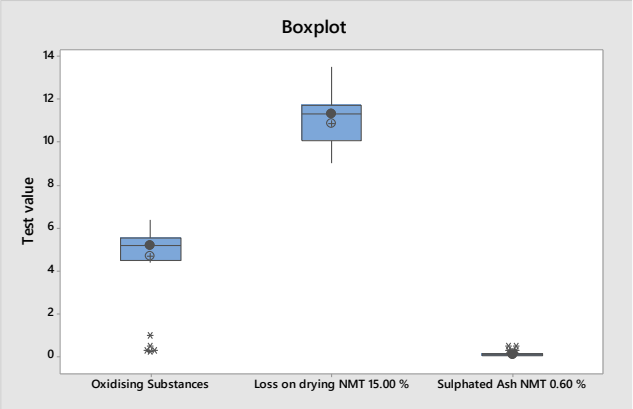

Figure 2. Box plot showing the examined inspection characteristics of corn starch showing data spreading's, means, medians and the presence of outliers

Table 2. Results of descriptive statistics of datasets for oxidizing substances, LOD, and sulphated ash using statistical software

Statistic	Oxidizing Substances	LOD	Sulphated Ash
Minimum	0.2500	9.000	0.0
25% Percentile	4.500	10.05	0.0500
Median	5.200	11.30	0.1000
75% Percentile	5.550	11.70	0.1300
Maximum	6.400	13.50	0.5000
10% Percentile	0.6000	9.360	0.0
90% Percentile	6.200	12.00	0.2800
Mean	4.691	10.87	0.1202
Standard Deviation	1.705	1.085	0.1126
Standard Error of Mean	0.2663	0.1695	0.01758
Lower 95% CI of Mean	4.153	10.53	0.08470
Upper 95% CI of Mean	5.230	11.21	0.1558
Lower 95% CI of Median	4.700	10.10	0.0900
Upper 95% CI of Median	5.300	11.60	0.1000

Control Charts and Examination of the Time-Series Pattern

No out-of-specifications (OOS) could be detected, although out-of-control states would be observed (Yu et al., 2018). The implementation of the trending charts based on the dispersion adjustment concept was used in Figures 3 to 5. The alarms were indicated with red dots and the meaning of each number could be tracked as generated by the program as the following (Pakdil, 2020):

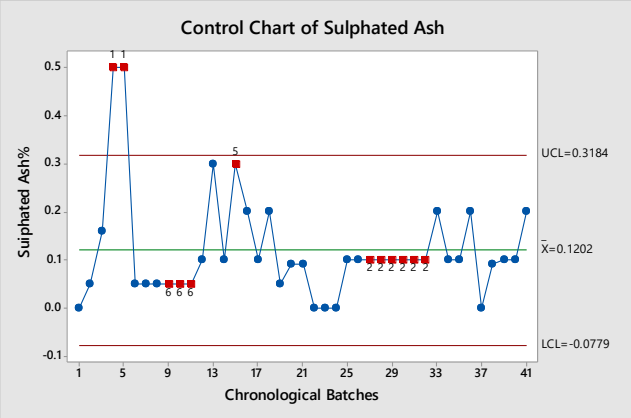

Figure 3. Process-behavior chart showing the common-cause, the assignable-cause variations, average line and the control limits for the sulphated ash test of the maize starch

Test Results for the Process-Behavior Chart of Sulphated Ash With Maximum Specification Limit of 0.60%

TEST 1: One point more than 3.00 standard deviations from center line (CL). Test Failed on points: 4, 5. TEST 2: 9 points in a row on same side of center line. Test Failed at points: 27, 28, 29, 30, 31, 32. TEST 5: 2 out of 3 points more than 2 standard deviations from center line (on one side of CL). Test Failed at points: 5, 15. TEST 6: 4 out of 5 points more than 1 standard deviation from center line (on one side of CL). Test Failed at points: 9, 10, 11. TEST 8. 8 points in a row more than 1 standard deviation from center line (above and below CL). Test Failed at points:11.

Test Results for the Process-Behavior Chart of LOD With Maximum Specification Limit of 15.00%

TEST 1: One point more than 3.00 standard deviations from CL. Test Failed at points: 3. TEST 2: 9 points in a row on same side of center line. Test Failed at points: 41. TEST 6. 4 out of 5 points more than 1 standard deviation from center line (on one side of CL). Test Failed at points: 15, 36, 38, 39.

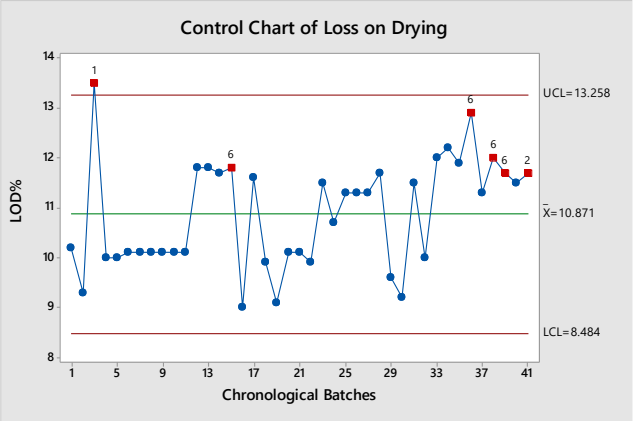

Figure 4. Process-behavior chart showing the common-cause, the assignable-cause variations, average line and the control limits for the loss-on-drying test of the maize starch

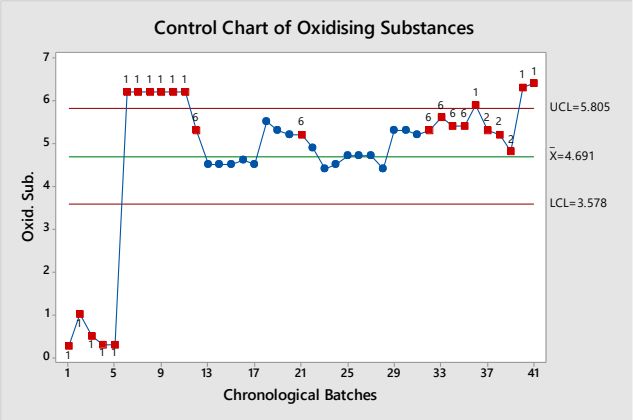

Figure 5. Process-behavior chart showing the common-cause, the assignable-cause variations, average line and the control limits for the oxidizing substances test of the maize starch

Test Results for the Process-Behavior Chart of Oxidizing Substances With Maximum Specification Limit of 20 ppm

TEST 1: One point more than 3.00 standard deviations from CL. Test Failed at points: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 36, 40, 41. TEST 2: 9 points in a row on same side of CL. Test Failed at points: 37, 38, 39, 40, 41. TEST 5: 2 out of 3 points more than 2 standard deviations from center line (on one side of CL). Test Failed at points: 2, 3, 4, 5, 7, 8, 9, 10, 11, 41. TEST 6: 4 out of 5 points more than 1 standard deviation from center line (on one side of CL). Test Failed at points: 4, 5, 9, 10, 11, 12, 21, 32, 33, 34, 35, 36, 37, 38, 40, 41. TEST 8: 8 points in a row more than 1 standard deviation from center line (above and below CL). Test Failed at points: 8, 9, 10, 11, 12, 36, 37, 38.

The three variables do not follow a normal distribution. This can be attributed to various factors, including: The inherent nature of the data: Some processes naturally generate non-normal data due to their underlying mechanisms. Outliers: Extreme values in the data can skew the distribution away from normality. Sample size: Smaller sample sizes can be less reliable in representing the true population distribution, and deviations from normality are more likely. Interactions: Complex interactions between variables can lead to non-normal distributions. Nevertheless, non-normality doesn't necessarily invalidate the use of control charts. Prioritization for investigating points that fall outside both the control limits and the specification limits: Points exceeding the specification limits (OOS) indicate a direct violation of the acceptable product quality standards and require immediate attention.

Points exceeding the control limits but falling within the specification limits (OOC) might represent potential process instability but don't necessarily translate to a product quality issue. However, they still warrant investigation to prevent future OOS occurrences. The alarm analysis mentions numerous out-of-control signals for all three control charts despite no "out-of-specification" (OOS) observations. While activating additional tests beyond the standard ±3 sigma limits can increase the chance of false alarms, it's crucial to balance this risk with the potential benefits of identifying true process issues. Justification for the use of additional tests – with caution - could be addressed through the following:

1. Acknowledgement of the increased risk of false alarms: Acknowledging the concern that using additional tests beyond +/- 3 sigma can lead to more false positives due to random chance.

2. The importance of identifying true process issues: The importance of not overlooking potential process problems that might not be captured by the basic ±3 sigma limits should not be underestimated. Early detection and correction of process issues can lead to improved product quality and reduced costs.

3. Justification for the use of specific tests: Clear justifications for each additional test used beyond the standard ones could be addressed through the following:

Test 2 (9 points in a row on one side): This test can be helpful in identifying trends or shifts in the process average, even if the individual points fall within the control limits. It can be particularly useful when dealing with autocorrelation (dependence of data points on previous observations) in the data.

Test 5 (2 out of 3 points beyond 2 sigma on one side): This test can be sensitive to sudden changes in the process variability, even if the individual points don't fall outside the control limits.

Test 6 (4 out of 5 points beyond 1 sigma on one side): This test can be used to detect shifts in the process variability even if the mean remains relatively stable.

Test 8 (8 points in a row above and below 1 sigma): This test can be helpful in identifying cyclical patterns in the data that might not be evident from the other tests.

4. The role of combined interpretation: It's crucial to interpret the results of all tests (both standard and additional) together, considering the specific context and historical data of the process. Relying solely on individual tests without considering the overall picture can lead to misinterpretations.

It is important for the investigator to be able to resolve the difference between "out of specification" (OOS) and "out of statistical control" (OOC) for several reasons:

1. Clarification of Control Limits vs. Set Specifications: OOS focuses on whether a single measurement falls outside the predetermined specification limits. Specifications are pre-defined boundaries that establish the acceptable range for a quality parameter. An OOS result indicates a potential deviation from the desired product quality. OOC deals with the statistical behavior of the data over time. It utilizes control charts, which set upper and lower control limits (UCL and LCL) based on the historical data's variability. An OOC signal occurs when a data point falls outside the control limits, suggesting the process might be experiencing increased variability or instability.

2. Distinguishing between Random Variation and Process Issues: OOS doesn't necessarily imply a problem with the process itself. It could be a random event or an isolated incident. Further investigation is needed to determine the cause of the OOS result. OOC signals a potential issue with the process. The data points falling outside the control limits suggest the process variability might be exceeding acceptable levels, potentially leading to inconsistent product quality.

3. Informs Decision Making: OOS might necessitate immediate action, such as retesting the sample or investigating the production line for potential causes. However, the decision depends on the severity of the deviation and the established quality control procedures. OOC often triggers a more in-depth analysis to identify the root cause of the process instability. This could involve adjustments to the process parameters, equipment maintenance, or implementing corrective actions to bring the process back under control.

Understanding the distinction between OOS and OOC helps to interpret quality control data more effectively, differentiate between random variations and potential process issues and make informed decisions regarding corrective actions and ensuring consistent product quality. An analogy to further illustrate the difference, the specification for manufactured device thickness might be 10mm +/- 1mm (between 9 mm and 11 mm). An OOS scenario would be a single, oddly thick (13 mm) single piece. While concerning, it might be a one-off mistake. However, OOC would occur if several units consistently fall outside the acceptable thickness range, indicating a potential issue with the procedure, manufacturing process or processing conditions.

In summary, some datasets fail to follow any distribution type, including the normal or Gaussian distribution, due to factors such as the inherent nature of the data, the presence of outliers or extreme values, small sample sizes, or complex interactions between variables. Since the monitored processes showed signs of out-of-control at several points, improvements are required to stabilize the inspection properties and control them. There are indicators for abnormal freak batches that exceed the control limits. Also, there are signals of mixed operations, early warning of trend shifts and over-control suggesting the presence of variable operations. Then, capability analyses could be conducted to determine the efficiency of the investigated characteristics. The foreign supplier should seek holistic quality improvement in the organization which would be pooled into the final manufactured raw products otherwise the quality aspects could be impaired in the long run.

CONCLUSION

The study employed various statistical techniques to evaluate the quality control aspects of a chemical compound. However, incorporating a correlation matrix would provide a more holistic understanding of the relationships between these aspects. The observed non-normal data distributions, outliers, and out-of-control signals in the control charts highlight the need for further investigation and process improvements to achieve consistent product quality and meet TQM goals.

The current work focused on three tests that are commonly used in most raw chemical materials. The implementation of SPC is crucial to evaluate the quality of the monitored inspection aspects of the chemical compound. The industrial governmental

agencies must supervise and monitor the flux of chemical goods using this methodology. However, till the enforcement and application of these rules, it is up to the final customers to take this responsibility and mandate the extension of these foundations to the primary source of these products. This is critical in the developing countries, especially when dealing with raw chemicals that are incorporated into healthcare, medicine, food and any products that could impact the health and even life of human beings in the country. If the concern about false alarms is significant, alternative approaches should be considered in the further future studies like using EWMA (Exponentially Weighted Moving Average) charts or CUSUM (Cumulative Sum) charts. These charts can be more sensitive to small shifts in the process mean while reducing the chance of false alarms compared to standard control charts with additional tests.

The present situation showed that despite the absence of any excursions in the inspected characteristics, the presence of several assignable causes of variations highlighted issues that need further investigations concerning the processing and manufacturing of the external manufacturer. This could lead to the necessity of the auditing routine to be implemented regularly to ensure GMP execution in the source company. The aberrant situations ranged from extraneous factors to shift and drift or even early warning for the deviation from the process mean. Moreover, the presence of trends, over-control and mixture patterns cannot be ruled out. This is a critical issue when considering raw components that would be incorporated into final manufactured products that would affect the health of the community, especially the sick and ill populations with their life dependent on the products' efficacy and safety. The study would embrace other inspection quality aspects and other raw chemical compounds in the future.

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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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Data Availability

The author confirms that the data supporting the findings of this study are available within the article.

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