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Enhancing Pharmaceutical Manufacturing through Statistical Process Control: An Industrial Engineering Approach to Quality Assurance

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ABSTRACT

In modern manufacturing, particularly within the process-driven healthcare industry, maintaining stringent control over critical quality attributes is paramount for ensuring product integrity and safety. This study demonstrates the application of Statistical Process Control (SPC), a core methodology in industrial and production engineering, to monitor and manage key process parameters: pH and the concentration levels of preservatives Methyl Paraben (MP) and Propyl Paraben (PP). Utilizing a comprehensive sixpack analysis, this research provides an engineering-focused framework for achieving optimal product quality. The study conducted a retrospective analysis of 184 measurements for each parameter from a healthcare product's routine quality control data. Due to the non-normal distribution of raw data, a Johnson SU transformation was applied to ensure the validity of the statistical analysis. The results revealed process instabilities despite some parameters showing acceptable capability indices (Pp and Ppk). The pH process was marginally capable (Pp=1.32, Ppk=1.21) but out-of-control, with a high defect rate. The MP assay showed good potential (Pp=1.70) and capability (Ppk=1.44) but exhibited instability, while the highly capable PP assay (Pp=2.00, Ppk=1.61) also showed signs of a process mean shift. This investigation demonstrated that while all tested products did not show out-of-specifications results, they pinpointed to the hidden signs of processes that need re-examination for significant improvements.

Keywords: Statistical Process Control (SPC), Industrial Engineering, Quality Engineering, Process Capability, Sixpack Analysis

1 Introduction

Maintaining the quality, safety, and efficacy of oral medical and pharmaceutical products is paramount in ensuring patient well-being and public health [1]. Among the various critical quality attributes (CQAs) that must be meticulously controlled, pH and preservative levels hold particular significance [2]. Specifically, Methyl Paraben (MP) and Propyl Paraben (PP) assays are crucial components to be tested for potency in healthcare products, particularly as preservatives [3]. Thus, it is important to embrace the reasons why these attributes require stringent monitoring, control, and assessment [4], emphasizing the importance of employing Statistical Process Control (SPC) methodologies, such as sixpack analysis, to achieve and maintain optimal product quality [5].

The significance of pH in oral pharmaceutical formulations is multifaceted [6]-[11]. Inadequate pH control can have detrimental consequences, as many active pharmaceutical ingredients (APIs) are susceptible to chemical degradation at specific pH levels [6],[7]. While specific pH limits are formulation-dependent and defined in the product's marketing authorization, general guidance for oral liquids often suggests a range between pH 4 and 7 to ensure API stability and patient comfort, although exceptions based on the drug's specific chemical properties are common. The solubility of an API is often pH-dependent, affecting bioavailability [8]. Furthermore, pH can influence the physical stability of formulations, affecting properties such as viscosity and aggregation, which can reduce shelf life [9]. Extreme pH values can cause irritation or discomfort, making it crucial to maintain pH within a physiologically compatible range, typically avoiding highly acidic or alkaline conditions (e.g., generally outside the 3-9 range for oral products to prevent mucosal irritation), for patient compliance [10]. pH also plays a role in preventing microbial contamination [11].

The importance of preservatives like MP and PP in oral formulations cannot be overstated [12]-[15]. They are added to inhibit the growth of microorganisms that can contaminate a product during its lifecycle [12],[13]. Microbial contamination can lead to product spoilage, health risks for patients, reduced shelf life due to the degradation of the API [14],[15], and significant regulatory non-compliance.

Given the critical roles of pH and preservatives, their levels must be tightly controlled throughout the product lifecycle [16]-[18]. This necessitates real-time monitoring, robust process control strategies, and comprehensive stability studies [16],[17] [18]. SPC provides a powerful set of tools for monitoring, controlling, and improving these processes [19],[20]. By using SPC techniques, manufacturers can detect special cause variation using control charts, assess process capability with indices like Pp and Ppk, reduce variability, make data-driven decisions, and ensure regulatory compliance [4],[19],[20].

The sixpack analysis, a comprehensive SPC tool, offers a holistic view of process performance by combining control charts, histograms, normal probability plots, and capability indices [19]. This investigation was conducted as an integral part of extensive research aimed at developing a robust improvement framework for the Quality Management System (QMS) in the pharmaceutical sector of economically poor nations. Thus, this research represents the application of industrial and quality engineering principles to enhance process control and ensure consistent product quality within existing production systems.

2 Materials and Methods

This study employed a retrospective analysis of process data for pH, Methyl Paraben (MP), and Propyl Paraben (PP) levels collected during routine quality control testing of a finished

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healthcare product. The dataset, sourced from a government-approved regulatory database in an Asian firm, consisted of 184 chronologically ordered measurements for each parameter, collected from consecutive batches during routine quality control testing of a finished oral liquid healthcare product. This retrospective data provides a longitudinal view of the process performance under normal manufacturing conditions. For acidity/alkalinity control by pH meter, the relationship between pH and hydrogen ion concentration [H+] is defined by the Eq. (1) [21]:

$$[H^+] = 10^{-pH} \quad (1)$$

This demonstrates the inverse logarithmic relationship where a lower pH indicates a higher concentration of hydrogen ions and vice versa [21]. On the other hand, the preservatives were analyzed chromatographically using High Performance Liquid Chromatography (HPLC).

2.1 Data Acquisition and Manufacturing Process Context

The data for this retrospective study were obtained from a finished product quality control database, which is maintained for regulatory compliance. As this was a retrospective analysis of an anonymized dataset, specific details regarding the analytical equipment (e.g., model, brand, and origin of the pH meter and HPLC system) were not available as they are kept private. The data for pH, Methyl Paraben (MP), and Propyl Paraben (PP) were collected from the final process quality control stage of a standard batch manufacturing process for an oral liquid pharmaceutical. The process involves the precise mixing of an active pharmaceutical ingredient (API) with various excipients, including the MP and PP preservatives, in a controlled environment. The pH is measured and adjusted at a critical step to ensure product stability, bioavailability, and patient comfort. The preservative concentrations are confirmed using HPLC post-formulation to ensure microbial efficacy throughout the product's shelf-life. The 184 measurements represent data collected from consecutive batches over a defined production period, making them suitable for assessing long-term process stability and capability.

2.2 Statistical Analysis

The statistical analysis was performed using Minitab® 17.1.0 (Minitab, LLC, State College, PA, USA) [22]. Prior to conducting process capability analysis, the distribution of the raw data for each parameter was assessed using the Anderson-Darling test and visual inspection of histograms and normal probability plots [23]. This assessment suggested that the raw data for all three parameters may not be best described directly by a normal distribution, with low p-values indicating deviations [24]. To address this, Johnson SU transformation was applied to the data for each parameter [25]. The Johnson SU transformation is a flexible three-parameter transformation used to normalize data in cases where a test for normality, such as the Anderson-Darling test, indicates a statistically significant deviation from a normal distribution (e.g., p-value < 0.05), or when visual inspection of a histogram suggests the presence of skewness, making the assumption of normality questionable [26]. Following the transformation, the normality of the transformed data was confirmed using the Anderson-Darling test and visual inspection.

The capability analysis in Minitab 17 was performed using the overall standard deviation to reflect long-term process performance. The control limits on the Individual (I) and Moving Range (MR) charts were calculated at the software's default of ±3 standard deviations from the process mean, which is a standard convention in SPC. The primary assumption, addressed by the Johnson transformation, was the normality of the data used for capability calculations.

2.3 Process Capability Analysis

Process capability was assessed using a sixpack analysis, which provides a comprehensive overview of process performance. For each parameter, the following metrics were calculated based on internal quality requirements [27]:

Pp (Process Potential): This index measures the potential capability of the process, assuming it is perfectly centered. It is calculated as the ratio of the specification width to the process spread (6 standard deviations) [28].

$Pp = (USL - LSL) / (6.\sigma)$

where USL is the Upper Specification Limit, LSL is the Lower Specification Limit, and σ is the overall process standard deviation.

Ppk (Process Capability): This index measures the actual capability of the process, taking into account both the process spread and its centering relative to the specification limits [29].

PPM (Parts Per Million): This represents the estimated number of defects per million units [30].

2.4 Control Chart Analysis

Individual (I) and Moving Range (MR) control charts were constructed for each parameter to assess process stability. Control limits were set at ±3 standard deviations from the process mean. The presence of any points outside these control limits was investigated as a potential indication of special cause variation. The last 25 observations for each parameter were specifically examined for any trends or patterns indicative of recent process shifts or drifts [31].

3 Results and Discussion

Process behavior charts for data often deviate from the assumed distribution required for suitable statistical processing, a frequent challenge in collecting raw process output [32],[33]The use of the Johnson SU transformation is justified by the non-normal distribution of raw data, ensuring the validity of parametric statistical methods. The sixpack analysis provides a robust framework for evaluating process performance, as supported by similar applications in related fields [5],[34],[35]. This approach allows for a data-driven assessment of the control and capability of pH, MP, and PP levels. The practical significance lies in its ability to assess and improve process capability in a real-world manufacturing setting. Even with transformed data, capability indices quantify how well the process performs, while control charts are invaluable for pinpointing specific instances of instability and guiding root cause analysis [36],[37]. This data-driven approach allows for proactive intervention to prevent larger quality issues and supports practical decisions about process adjustments, maintenance schedules, and operator training [38],[39]. The sixpack approach provides a holistic overview of the inspection characteristics under investigation, as demonstrated in previous studies [28].

3.1 Sixpack Analysis for pH

Before analyzing the results for the pH process, it is crucial to clarify the Y-axis of the I-chart in Fig. 1. Since the raw data was non-normal, the statistical control analysis was performed after applying Johnson SU transformation. Therefore, the values plotted on the I-chart's Y-axis represent the transformed, normalized data points, not the original pH values. This mathematical transformation centers the data around a mean near zero, resulting in both positive and negative values, and it allows for the valid application of control limits based on a normal

distribution. The sixpack analysis of the pH process, shown in Fig. 1, reveals a process that is out-of-control. While the capability histogram and normal probability plot suggest a normal distribution after transformation, the I and MR charts indicate significant issues with process stability and variability. The I chart shows numerous points exceeding the control limits, suggesting the process is experiencing significant fluctuations. It should be noted that 43 points on the I chart and 13 on the MR chart exceeded control limits, suggesting significant issues that require deeper investigation. The process capability index (Pp) of 1.32 indicates the process is marginally capable, and the Ppk value of 1.21 confirms this, especially given the out-of-control points. The parts per million (PPM) defectives are 154.93, indicating a relatively high defect rate. The alarms on the I chart for the last 25 observations suggest the process is shifting significantly, contributing to its declining capability [36][37] [5].

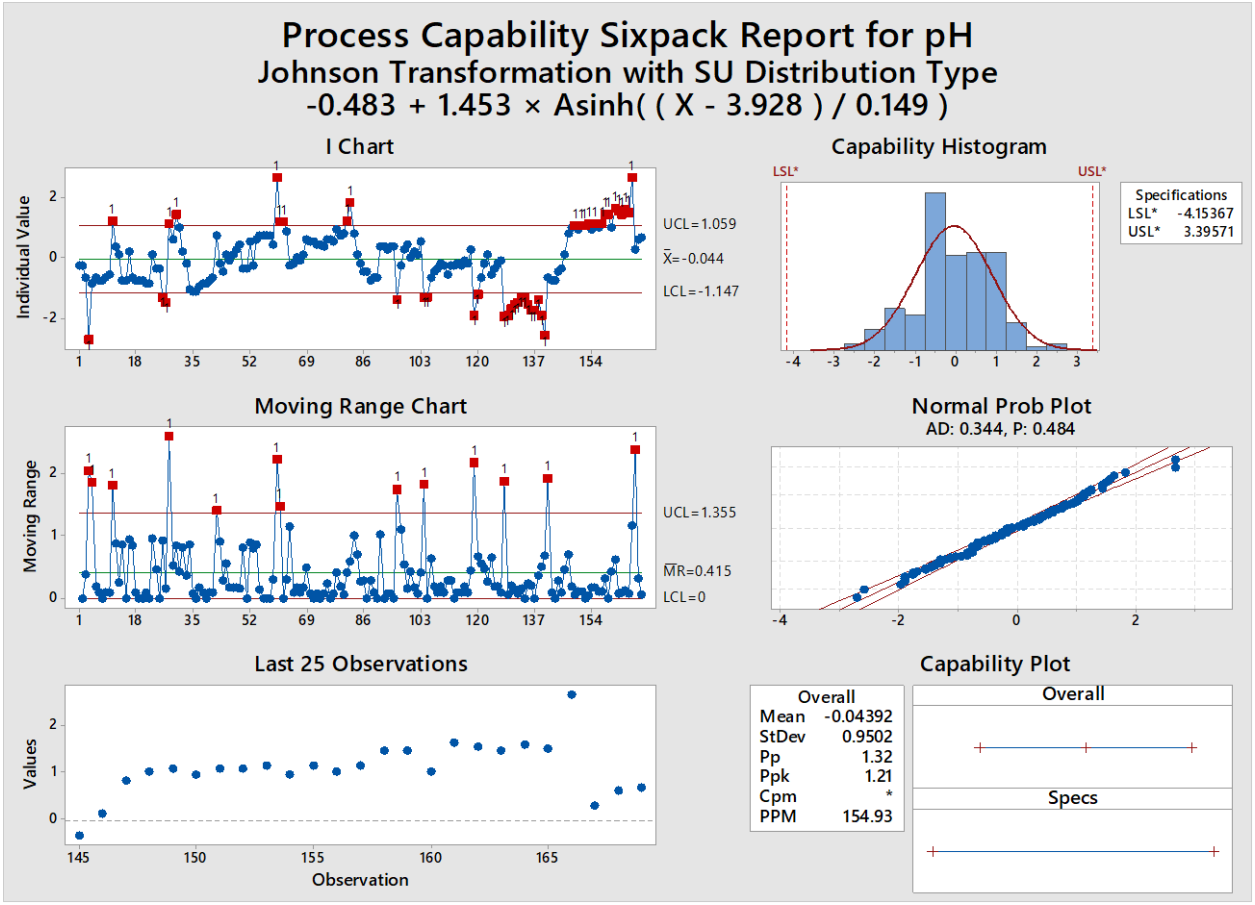

Fig. 1 Sixpack Analysis for pH Process. This report shows significant instability via out-of-control points on the I and MR charts. The process is only marginally capable (Ppk=1.21) with a high defect rate, necessitating process improvement.

3.2 Sixpack Analysis for MP Assay

The sixpack analysis for the Assay of MP (Fig. 2) reveals a process that is capable but exhibits some signs of instability. The I chart displays four individual points exceeding the control limits, and the MR chart shows three excursions above its upper control limit, suggesting abnormal variations. The Pp value of 1.70 indicates that the process has good potential to meet specifications, while the Ppk value of 1.44 reveals the process is not perfectly centered. The combined information from both charts highlights that the process is not in a state of statistical control. A generally declining trend in the last 25 observations is particularly noteworthy as a potential shift in the process mean, raising doubts about the long-term reliability of the process. It is crucial to investigate the causes of the high values and the potential shift in the mean to stabilize the process before relying solely on capability indices [36],[37],[40]

3.3 Sixpack Analysis for PP Assay

The sixpack analysis for the Assay of PP, presented in Fig. 3, shows a process that is highly capable but exhibits signs of instability. The I chart reveals several individual points exceeding the control limits, and the MR chart shows five points outside its limits, suggesting that short-term variability is likely unstable. The capability indices are excellent, with a Pp value of 2.00 and a Ppk of 1.61. These values significantly exceed the common industry acceptance criterion of Ppk 1.33, which confirms the process is highly capable of meeting specifications. However, the control charts reveal that the process is unstable. Specifically, several data points on the I chart fall outside the calculated ±3 standard deviation control limits, and five points on the MR chart exceed its upper control limit. These out-of-control points are direct evidence of special cause variation and instability, demonstrating that although the product remains within specification, the process itself is not reliable or predictable. The last 25 observations show several alarms and a clustering of values, suggesting a potential recent shift or drift in the process mean. This instability is a strong indicator that the process is not reliable long-term, even with acceptable capability indices. The off-centering indicated by the difference between Pp and Ppk should also be addressed to optimize the process.

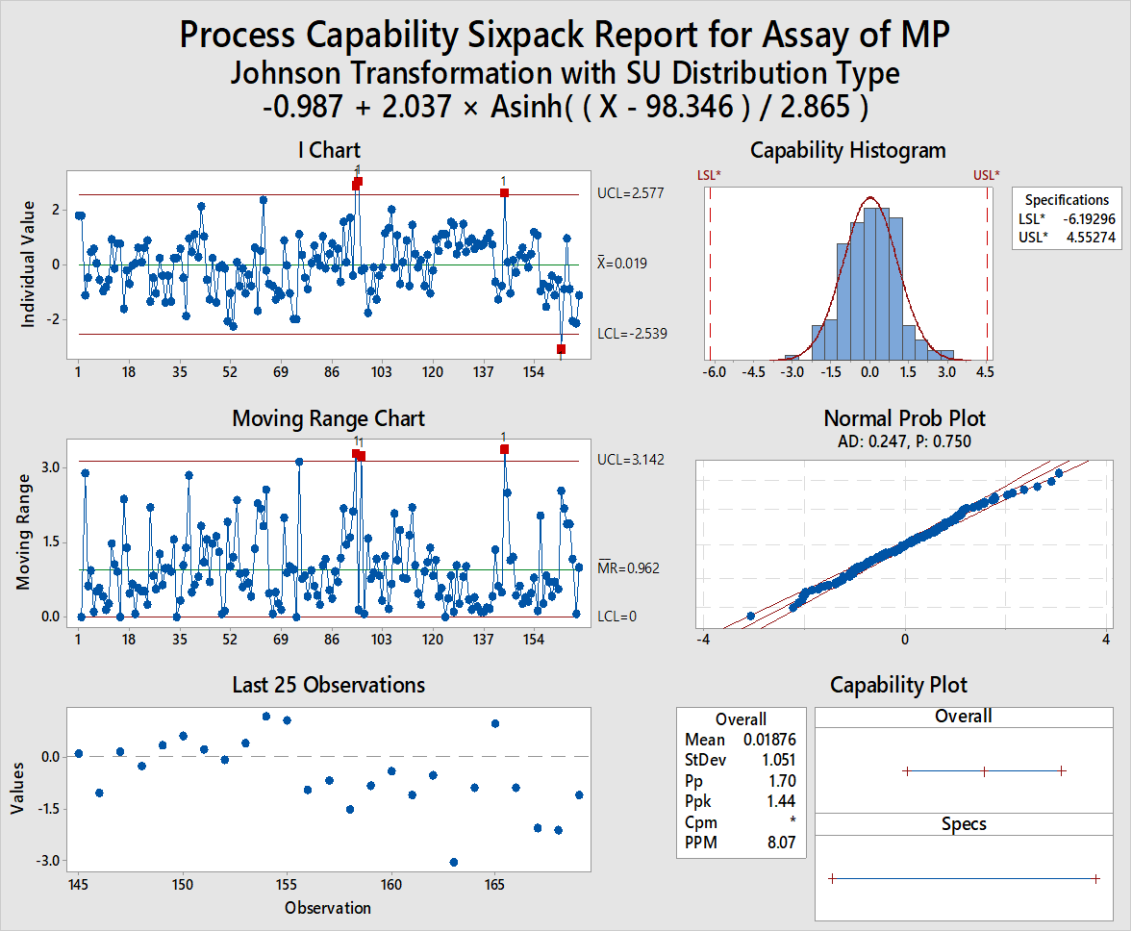

Fig. 2 Sixpack Analysis for MP Assay. This report indicates a capable (Pp=1.70, Ppk=1.44) but off-center process with signs of instability. Out-of-control points and a potential mean shift in recent data require corrective action.

3.4 Cause and Effect Analysis

The inconsistent control of pH, MP, and PP levels necessitates a comprehensive investigation using a tool like the Ishikawa (Fishbone) analysis, with potential causes categorized as shown in Table 1. Potential causes include measurement system deficiencies [41],[42], human factors [43], method-related issues [44],[45], equipment-related problems [46], material-related factors [47], and environmental influences [48].

The primary concern is the unstable process variability evident in the control charts. This may be caused by inconsistent mixing, temperature variations, or raw material fluctuations [41],[42],[46]. Although capability analysis can be performed on out-of-control processes, the results may not be reliable [49]-[51]. To obtain a reliable assessment, it is essential to first identify and eliminate the special causes of variation to bring the process into a state of control [49]-[51].

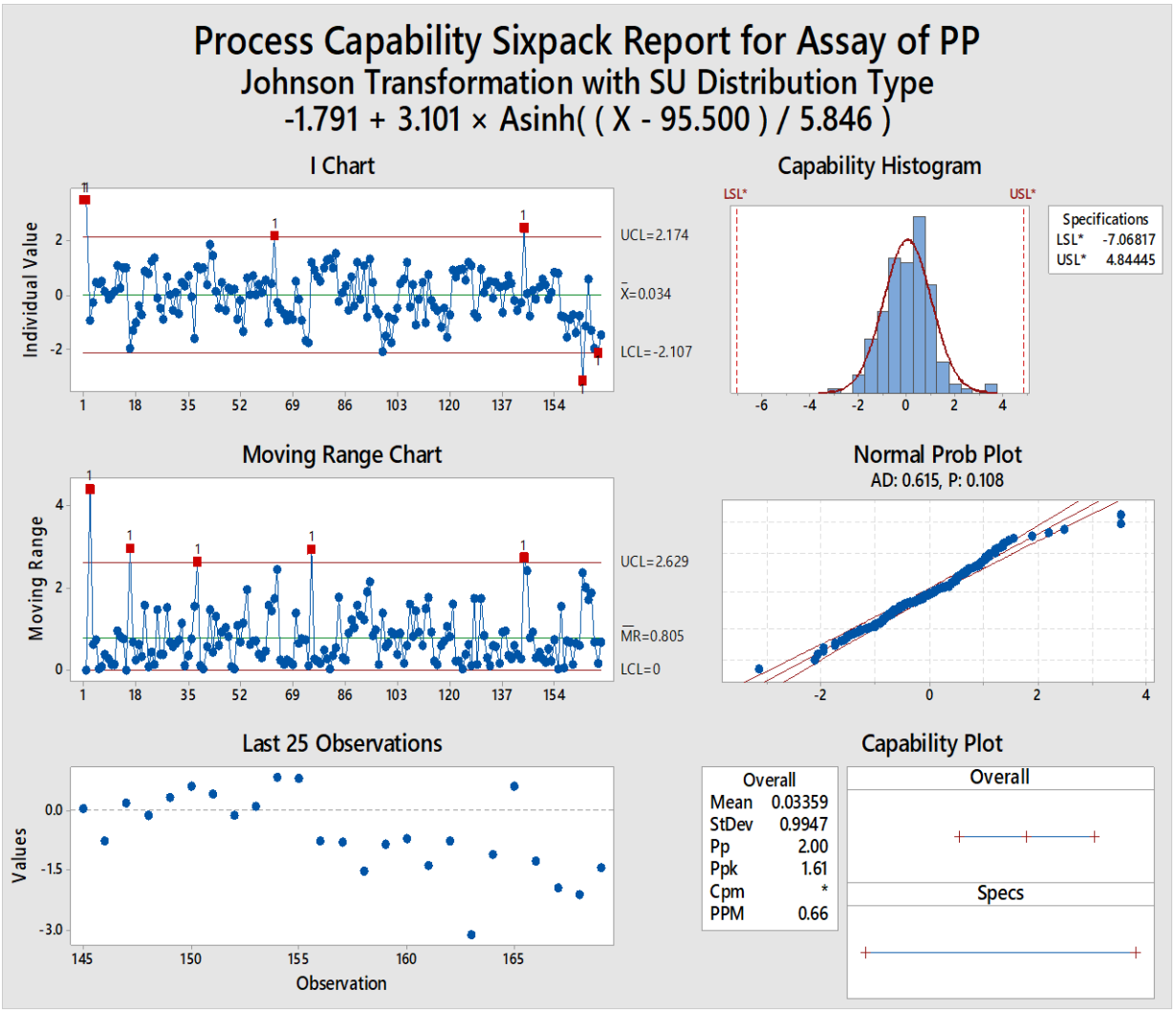

Fig. 3 Sixpack Analysis for Assay of PP. The analysis shows a highly capable process (Pp=2.00, Ppk=1.61). However, the I and MR charts reveal out-of-control points, indicating statistical instability that requires investigation.

Table 1 Range of potential causes and sub-causes for inconsistent control of pH, MP, and PP levels.

Category*	**Cause**	**Sub-cause**
	Inaccurate Instruments**	Calibration, Faulty Equipment, Maintenance
Measurement	Sampling Errors	Representative Samples, Technique, Contamination
	Operator Error	Inconsistent Technique, Training, Human Error
	Inadequate Training	Process Control, Equipment, Procedures
Man	Human Error***	Weighing, Mixing, Adjustments
	Lack of Awareness	Importance of Limits
	Inadequate Procedures	Definition, Standardization, Outdated
Method	Process Variability£	Mixing, Temperature, Raw Materials
	Lack of Optimization	Design, Control, Monitoring
Machine	Equipment Malfunction€	Sensors, Pumps, Dispensing
	Maintenance Issues	Preventive, Calibration
	Raw Material Variability	Quality of Water, Ingredients
Material	Storage Conditions	Heat, Moisture, Degradation
	Supplier Issues	Consistency, Quality Control, Supply Chain
	Temperature Fluctuations	Seasonal Changes, HVAC System Issues, Poor Insulation
Environment	Humidity	Weather Conditions, Ventilation Problems, Equipment Leaks
	Contamination	Airborne, Dust, Microorganisms

* Table follows Fishbone or Ishikawa diagram concept in identification of the spectrum of the potential causes for the observed defect(s).
** pH probe calibration drift, incorrect buffer standards, HPLC column degradation
*** Incorrect weighing of preservatives, improper pH adjustment technique, inconsistent sample withdrawal
£ Inadequate mixing time/speed, temperature fluctuations affecting solubility, variability in raw material lots
€ Faulty pH electrode, malfunctioning mixer impeller, residual cleaning agents in the tank

4 Conclusion

Capability analysis is a valuable tool for monitoring finished product quality, but it must be used with caution when a process is out-of-control. A thorough investigation of the out-of-control points and observed process variability should be conducted to identify the root causes of the inconsistent control and capability of pH, MP, and PP levels in future studies. Potential sources of the increased and unstable process variability, such as inconsistent mixing, temperature variations, and changes in raw material quality, should be investigated. Equipment malfunction, raw material variability, and the measurement system itself should also be assessed. Additionally, operator techniques and adherence to standard procedures should be reviewed to minimize human-factor variability. Following the investigation, appropriate corrective actions must be implemented to address the identified root causes, including optimizing process controls, improving equipment maintenance, and ensuring raw material quality. The effectiveness of these actions should be verified through ongoing monitoring of control charts and capability indices, and the process should be continuously monitored for long-term stability.

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Author Contributions

M. Eissa: Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization.

Conflict of Interest Statement

The author declares no competing financial or non-financial interests, nor any personal relationships, that could influence the work reported herein.

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Data Availability

Data will be made available on request.

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