**Original Research Article**

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**TRENDING PERSPECTIVE IN EVALUATION OF INSPECTION CHARACTERISTICS OF PHARMACEUTICAL COMPOUND: COMPARATIVE STUDY OF CONTROL CHARTS**

**ABSTRACT**

**Background and objectives:** The quality and efficacy of the pharmaceutical medicinal product are of paramount importance to the patients. Reproducibility and consistency of the properties of the dosage form start with the constituting ingredients either active or inactive. The present work provides an approach for the trending of one of the crucial inspection characteristics of a well-known excipient that is commonly used as a disintegrant of a water-insoluble synthetic cross-linked Polyvinyl Pyrrolidone (PVP). Establishing manufacturing criteria and quality limits should be assessed from the beginning level of the project using exploratory process-behavior plots.

**Materials and Methods:**This study involved an assay of the initial 16 batches of the manufactured 1-ethenyl pyrrolidine-2-one expressed as a dried substance using a standard analysis method according to British Pharmacopoeia (BP). Exploratory Shewhart charts were plotted after preliminary distribution identification using Statistical Process Control (SPC) software. Based on the goodness of fit test results, the most appropriate assumed distribution was implemented in drawing the Individual-Moving Range (I-MR) control charts.

**Results:**The goodness of fit study and probability plot showed that the most close-fitting to the data dispersion pattern was Johnson transformation to the normal spreading, smallest extreme value and Weibull distribution, respectively. While there were no alarms that could be detected from the process mean and the variability charts, further improvement is required from the supplier side to meet the benchmark minimum limit threshold, in addition, the process mean was not centered but shifted towards the Upper Control Limit (UCL).

**Conclusion:**Implementation of SPC techniques is crucial in the modern competitive healthcare industry. Trending charts play a pivotal role in this perspective.They provide a quantitative estimation for the current situation and the actions needed for the future improvementof the monitored characteristic.

**Keywords:**Control charts, probability plot, Johnson transformation, capability plot,smallest extreme value, Weibull.

**INTRODUCTION**

In the world of competitive healthcare and the pharmaceutical industry, many companies and firms compete in the drug and medicinal products market.1-3 However, safety, quality and efficacy come as the first-place priority of the patient Health.4-6 Medicinal ingredients either active or inactive should be the cornerstone for the standard quality before the analysis of the inspection properties of the finished medicinal dosage forms.

Implementation of the statistical Process Control (SPC) methodologies has become a crucial and commonly practiced task in all pharmaceutical firms to achieve a high level of predictable and acceptable quality.7-9 One of the most pivotal SPC tools is the Shewhart plot.10 It has vast applications in many industrial and non-industrial areas to assess and control processes and inspection characteristics.11-15 The manufacturers of the raw chemicals of pharmaceutical grades have expanded worldwide making them easy to be attained in the retail markets and brokers anywhere.16 Nevertheless, sustainable quality assurance of the expected chemical and physical properties is of paramount necessity to guarantee the current and the future merit of the pharmaceutical products.

There are growing trends in the number of chemical manufacturing facilities, notably in the developing nations. The Good practices in various fields (GxP) status of them – including the medicinal and healthcare sectors - are questionable.17,18 Good Manufacturing Practice (GMP) could be projected into the quality of the final product.19 Hence, an organization with the right quality concept in mind throughout the whole firm would yield products with acceptable, stable and predictable properties with minimal risk of failure.

In a time of crisis, there is a great possibility of witnessing degradation in the quality of goods that are available from the brokers, wholesalers and market retailers to meet the demand of the customers with low prices at the expense of the essential quality inspection characteristics. Due to the emphasized challenges, the present work aimed to evaluate the fineness and goodness of a selected excipient that is commonly incorporated in pharmaceutical preparations from chemical manufacturing companies. The study will focus on an important test that is officially considered one of the critical inspection properties of inactive material.

**MATERIAL AND METHODS**

A chemical manufacturing plant of raw materials of pharmaceutical grade was assessed for the quality of the manufacturing output.16,17Sixteenbatches of one of the common excipient materialswere investigated for the assay result trend.16,17The inactive material - which is commonly known to be used as a thickening agent,solubility enhancer, disintegrant and emulsifier – is an insoluble polyvinyl pyrrolidinone polymer that is crosslinked or Polyvinylpyrrolidone (Crospovidone) with the chemical formula (C6H9NO)n.

According to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature, it is named 1-Ethenylpyrrolidin-2-one.20Each manufactured batch was subjected to the analysis using the standard official method of the British Pharmacopoeia (BP).21 The assay limit is 11.0 - 12.8 % of nitrogen based on dried substance.21 The preliminary assay data was analyzed using Minitab version 17.0 to screen for the distribution fitting and to constructan appropriate SPC examination profile.22-25 Based on the output results, the initial state of control could be determined from the control charts, capability analyses and histograms.

The assay was conducted as follows: In a combustion flask, 0.100 g of the material to be tested (m mg) was added, five g of a mixture consisting of one g of copper sulfate pentahydrate R, one g of titanium dioxide R, 33 g of dipotassium sulfate R, and three glass beads.21 A tiny amount of water R was used to wash any clinging particles from the neck into the flask. Seven milliliters of sulfuric acid R were poured and allowed to trickle down the flask's inner wall.21 The flask was heated gradually until the solution was a clear, yellowish-green hue and there was no carbonized material on the interior wall. Then, the flask was heated for an additional 45 minutes.

Once the flask has cooled, the content must be poured carefully into 20 mL of water R. The flask should be attached to the distillation equipment, which has already been cleaned by running steam through it.21Thirty mL of a 40 g/L boric acid solution R, 0.15 mL of a bromocresol green-methyl red solution R and enough water R should be added to submerge the bottom end of the condenser tube in the absorption flask.21Thirty milliliters of strong sodium hydroxide solution R should be poured through a funnel; the funnel is rinsed gently with ten milliliters of water R; the clamp must be shut on the rubber tube right away; and the steam distillation process must be started to extract 80–100 milliliters of distillate.

After taking out the absorption flask from the condenser tube's lower end and washing the end portion with a small amount of water R, the distillate was titrated with 0.025 M sulfuric acid until the solution's color shifted from green to pale greyish blue to pale greyish red purple.21 Any necessary corrections were to be made after performing a blank measurement.

**Statistical analysis**

**RESULTS AND DISCUSSION**

This project is part of a total examination of the organization to achieve the Total Quality Management (TQM) goals of the chemical plant.26,27Errors in production are continuously detected, reduced, or eliminated through the process of total quality management (TQM).27 It guarantees that staff members receive the most recent training, expedites supply chain management, and enhances customer satisfaction.27 Holding everyone engaged in the manufacturing process responsible for the overall caliber of the finished good or service is the goal of total quality management.

Detailed dispersion pattern of the dataset using probability plots are shown in Figures 1 and 2. The goodness of fit test demonstrated that only three distributions are valid in the following descending order: Normal (after Johnson transformation), smallest extreme value and Weibull. The selection was based on Anderson-Darling (AD)the goodness-of-fit figureprobability charting and the p-values.





**Figure1: Probability distribution identification showing the goodness of fit test to exponential, two-parameterexponential, Weibull, three-parameter Weibull, logistic, log logistic, three-parameter log logisticand Johnson transformation to normal distribution.**





**Figure 2: Probability distribution identification showing the goodness of fit test to smallest extreme value, largest extreme value, gamma, three-parameter gamma, normal, Box-Cox transformation to normal distribution, lognormal and three-parameter lognormal.**

A probability called the p-value assesses the strength of the evidence against the null hypothesis.28 The null hypothesis for an AD test is that the data are distributed as expected.29 Lower p-values thus offer more proof that the data do not fit the distribution.

The preliminary exploratory Individual-Moving Range (I-MR) process behavior charts in Figures 3, 4 and 5 showed stable variations and process means according to the selected types of the best-fitting distributions. Each corresponding dispersion was acceptable according to the probability plot.30-31Moreover, the capability histograms illustrated that the spreading of data was confined within the Upper Specification Limit (USL) and the Lower Specification Limit (LSL).32 In addition, the bins' dispersion frequency is close to the hypothetical presumed underlying distribution assumption.33 It is evident that the process average is not centered in the middle of the specification window, instead it showed that the preliminary results are all above the centerline risking an excursion above the upper threshold.

The sample mean ± the overall standard deviation was approximately ≈ 12.5 ± 0.19. In the capability analysis, the width of the inspection characteristic variation i.e., the Voice of Process (VoP) should be less than the Voiceof Customer (VoC).34Ppk is the index for performance centering.35It gauges the degree to which the data is centered inside the specified bounds. The resultant values in Figures 3, 4 and 5 lie within 1.00 and 1.33.36 This is in the middle of the road and more improvement should be made to achieve the benchmark target value. On the other hand, Pp is the index of performance.35,36 It gauges the degree to which the data could fit inside the specified bounds (USL, LSL).35,36 Nevertheless, it doesn't matter if it is centered within the boundaries window. In this case, it is obvious that the inspection characteristic of the assay results yielded satisfactory results in terms of the overall capability examination study.

Z.bench (overall) is the percentile that converts the predicted probability of process defects to an upper tail probability on a standard underlying assumed distribution.37 It is computed using the overall standard deviation and is dependent on the overall performance of the process.37 While Z.LSL was acceptable, Z.USL showed values below Z.bench.The predicted percentage of parts outside of the specified limitations is the percent total for expected overall performance. Calculating the expected value involves utilizing the total standard deviation. The probability that the measurement of a randomly chosen portion from the overall process distribution is beyond the specified bounds is the percentage total for predicted overall performance.

Based on the overall variation of the monitored process, the percentage above USL is used for predicted overall performance to estimate the percentage of nonconforming products that might be expected to be above the upper specification limit.38 The actual process performance that the inspection property experiences over time is indicated by the overall performance values.38 In comparison to the maximum specification limit, lower values of the percentage over USL indicate more process capability. Few or no parts should have measurements that are higher than the highest limit of the specification. The same could be extrapolated for the percentage below LSL.





**Figure 3:Process capability six-pack of the assay using Johnson transformation to the normal distributionusing transformation function γ + η ln [(x – ε) / (λ + ε – x)] for Johnson family distribution with the variable bounded {B}(SB) with a range of η, λ > 0, –∞ < γ <∞, –∞ < ε < ∞, ε < x < ε + λ.**





**Figure 4: Process capability six-pack of the assay using smallest extreme value distribution.**





**Figure 5: Process capability six-pack of the assay using Weibull distribution.**

It should be emphasized that establishing statistical quality monitoring from the beginning of the manufacturing process for chemical production is a mandatory activity that should not underestimated to ensure obtaining raw materials with stable, predictable and conforming inspection properties indicating a Good Manufacturing Practice (GMP) during the production processes.39 It is important to implement GxP for any reputable company to take the lead in any competitive market where the common acronym for quality standards and recommendations that are considered to be "good practice" is GxP.40 The different areas it can be applied to are represented by the "x". GxP is an abbreviation that is frequently used to describe a group of quality standards. The quality of the single components would be reflected in the functioning values of the final dosage forms. This is crucial when considering the health and life of the patients in the world of ever-growing populations of sick individuals.

**Limitations of the study**

**CONCLUSION**

Process-behavior plots based on the non-normally distributed datasets showed the quality of the manufactured raw material did not demonstrate out-of-control states between the successive batches. However, the process capability monitoring showed that the performance needs improvements and tightening in the variations of the inspection characteristic (assay) between consecutive products is essential to achieve better performance index level.Moreover, the average line is shifted towards the USL. Accordingly, the mean of the process should be brought close to the center to avoid any risk of out-of-control results above the upper limiting threshold in the future.

**RECOMMENDATIONS**

Further research studies with other inspection characteristics of the pharmaceutical raw material should be conductedand other medicinal ingredients produced by the manufacturer should be included. Moreover, the investigationwould embrace all the chemicals produced by the drug manufacturing company as an integral part of the quality improvement system.

**CONFLICT OF INTERESTS**

The author does not have any conflict of interest.

**Author’s Contribution**

**ACKNOWLEDGEMENTS**

None to declare.

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