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Short communication

Systematic approach for proper control chart design for Karl-Fischer titrator

Blagoj Achevski*, Frosina Arsova, Jelena Acevska, Jasmina Tonikj-Ribarska, Katerina Brezovska, Natalija Nakov

[1]*Faculty of Pharmacy, University "Ss Cyril and Methodius", 1000 Skopje, Republic of North Macedonia*

Introduction

Statistical Process Control (SPC) is an essential part of quality assurance in many industries, including the pharmaceutical industry (Eissa & Abid, 2018; Shah et al., 2010; Velinovska et al., 2019). This methodology promotes better understanding of the source of variation of a particular process, thus contributing for its continuous improvement. Control charts (CC), as one of the main SPC tools, allow monitoring of the process variability over a period of time and detection of the systematic (common) causes of process variation (ISO 7870-1, 2019). The application of CC is expanding from the manufacturing departments of the pharmaceutical industry to the quality control analytical laboratories. CC are used for monitoring the method/instrument performance, thus may indicate the need for re-qualification of the instrument; instability of the reference material; errors in the calculation of the analytical result; insufficient training of the personal, etc. (Sengoz, 2018). The basic elements of the CC are the center line (CL) and upper and lower control limit (UCL and LCL, respectively) (ISO 7870-2, 2013). The choice of the suitable type of CC, along with the proper establishment of the UCL and LCL have great impact on the sensitivity of the CC. In case of evaluation of improperly designed CC, there is a possibility to overview a process that is really out of a statistical control, or in opposite scenario a process that is under control might be detected as an out of statistical control. Hence the need for proper design of the CC is demanded for accurate evaluation of the process variability.

The aim of this research is to establish a systematic approach for proper design of CC for monitoring the performance of instruments used in quality control analytical laboratory. The systematic approach for selection a suitable CC, establishment of CL and use of adequate rules for evaluation of CC will be shown using instrument for semi-micro determination of water i.e. Karl-Fischer (KF) titrator as an example.

Materials and methods

Materials

The semi-micro titration of water was performed on Karl Fischer Titrator DL38, Mettler Tolledo. Aquastar CombiTirtant 5mg/mL (Supelco) was used as a titrant and Aquastar CombiMethanol (Supelco) as a solvent. The Water Standard 1% (10 mg H_2O/1 g) CRM (Merck) was used for performance verification of the KF titrator.

The data for the percentage recovery (r, %) of water, obtained after addition of Water Standard 1%, were used for design of different types of CC and calculation of the control limits. Each data point in CC represents the mean r (%) of three independent additions of Water Standard 1%. The 100% recovery was chosen as a CL for the X-chart, whereas the mean value of the r (%) obtained from 26 determinations was used as a CL for J-chart. The CL of the CC were created using 26 data points of and additional 12 data points were used for further instrument performance monitoring.

Results and discussion

The first step in the systematic approach for proper CC design is selection of suitable type of CC. Suitable CC for monitoring quantitative data for grouped results (n=3)

*bachevski@ff.ukim.edu.mk

are X-chart, R-chart or J-chart (zone control chart). The evaluation has shown that X-chart is sensitive for changes of the mean and standard deviation (σ) of the determination. However, this type of chart doesn't provide information about the distribution of the individual data in the subgroups. This kind of information could be obtained with the R-chart. However, the R-chart only takes into account the within-run precision of the determination. Considering that the performance of the KF titrator is evaluated through the accuracy of the determination (recovery), the X-chart was found to be more suitable for performance monitoring of the KF titrator than the R-chart. The evaluation of the J-chart confirmed that this kind of CC incorporates the characteristics of the X-chart and the CUSUM chart. This kind of chart is efficient in detection of rapid changes of the determination, thus could be applied for the performance evaluation of the KF titrator.

The second step is defining the UCL and LCL of the CC. Therefore, several X-charts were designed using different approaches for defining the CL. The first activity is evaluation whether the data points show normal (Gaussian) distribution or not. The obtained values of the statistical parameters Skewness and Kurtosis (-0.23 and -0.76, respectively) confirmed that the data points show normal distribution, thus the use ±3σ (±3*0.91) as UCL and LCL (103.16 and 97.19, respectively) for the X-chart was justified. In addition, another X-chart using $\pm 3\sigma_{total}$ value (±3*0.85) as a UCL (102.54) and LCL (97.46) was designed. The σ_{total} includes the within-run (variance within the subgroup of results) and between-run variance (variance between all subgroup of results). The results showed that in case where X-chart is created with data points of group data, defining CL by means of σ_{total} is more appropriate. Considering the recovery tolerance limits given in the OMCL Qualification of equipment guideline (GEON, 2022), another X-chart was designed using the values of 97.5% and 102.5% as UCL and LCL, respectively. The evaluation of the sensitivity has shown that the use of the tolerance limits from the guideline as CL, reduces the sensitivity of the X-chart to raise the alarm in case the instrument gets out of a statistical control.

The σ value needed for defining the CL of the J-chart was calculated by multiplying the moving range with 0.8865 (AMCTB, 2003). The obtained values for UCL and LCL of the J-chart were 103.23 and 97.27, respectively. Although these CL are wider than the CL defined for the X-charts, the sensitivity of the J-chart was not brought in question. The reason for the better sensitivity of the J-chart compared to the X-chart with 97.5% and 102.5% as CL, might be the existence of different set of rules for evaluation of the J-chart.

The designed CC were applied for instrument performance monitoring. The results showed that WECO rules, as well as Westgard combined rules could be applied to the evaluation of the X-chart using ±3σ or $\pm 3\sigma_{total}$ value as CL. Whereas, only three WECO rules (1_{3s}, 2_{2s} and 9_x) are applicable for the evaluation of the X-chart using tolerance limits as CL. The J-chart couldn't be evaluated using WECO rules or Westgard combined rules.

Conclusion

This research showed that the proper selection of the type of CC; proper defining of the UCL and LCL; as well as evaluation of the CC using adequate rules, has a direct impact on the sensitivity of the CC and the accuracy of the evaluation of the instrument performance. The proposed systematic approach for the proper CC design for monitoring the performance of the KF titrator could be applied for designing CC for different instruments, depending of the needs of the analytical laboratories. This research could contribute towards expansion of the application of the CC as a part of the quality assurance system in analytical laboratories for quality control.

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