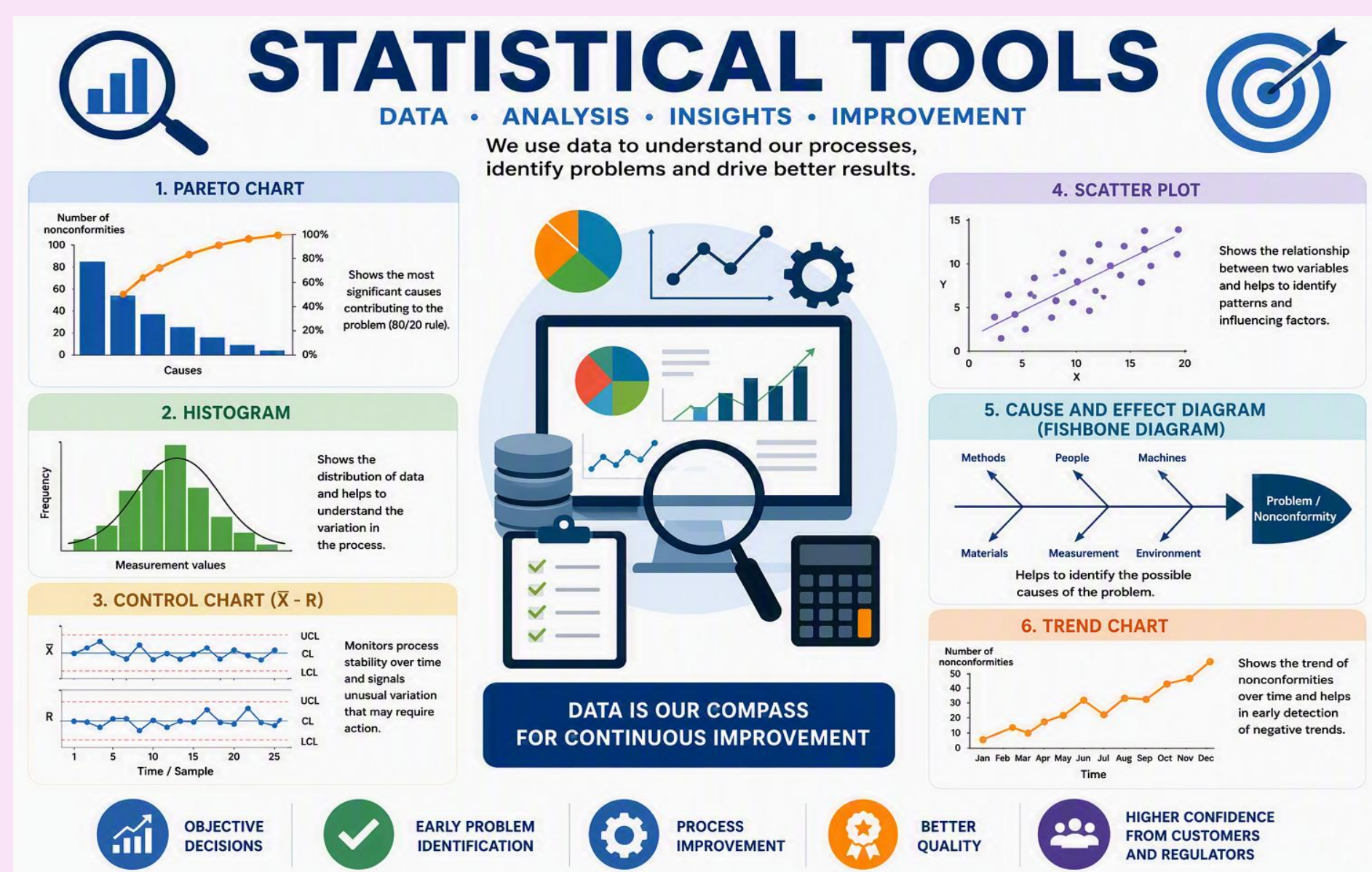


APPLICATION OF STATISTICAL TOOLS FOR TREND ANALYSIS OF NON-CONFORMITIES: EXPERIENCE FROM ALKALOID

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Introduction & Aim



Statistical tools provide a scientific and objective approach to the processing and interpretation of data related to nonconformities. Their application enables the determination of whether specific occurrences are random or indicative of a systemic issue, whether there is an increasing trend in deviations, and which factors contribute most significantly to their occurrence. The primary objective of nonconformity trend analysis using statistical tools is to ensure systematic monitoring, evaluation, and interpretation of data in order to timely identify adverse trends and implement appropriate measures to prevent and reduce their occurrence. By applying statistical tools, organizations can transition from a reactive to a proactive approach in nonconformity management, resulting in improved process efficiency, enhanced product quality, and a higher level of confidence among customers and regulatory authorities.

Experimental



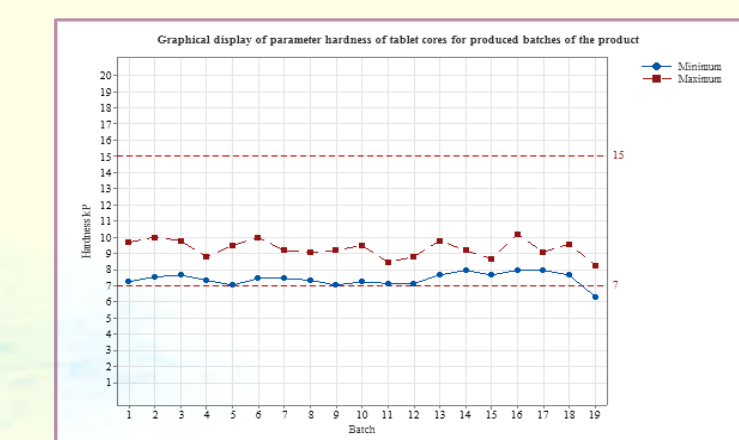
Figure 1. Measuring instrument Erweka Hardness Tester



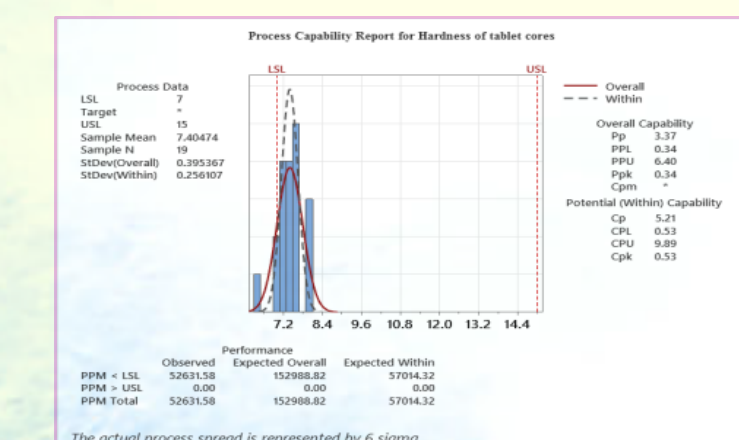
During the production of a commercial batch of a product – inhibitor of HMG-CoA reductase, during the implementation of process control in the tableting phase, values for the parameter hardness of tablet cores outside the specification limits were obtained. Values from a minimum of 6,32kP (61,97N) to a maximum of 8,26kP (81,00N) were obtained, while the specification limits are: 7 – 15kP (68,64N – 147,1N). The instrument that was used for the testing of parameter hardness of tablet cores is Erweka Hardness Tester. For the purposes of the investigation, a statistical evaluation of the parameter hardness of tablet cores in previously produced batches of the product was carried out using statistical tools Process Capability, Cpk, Histogram, Line Plot, Descriptive statistics and Control limits.

Figure 2. Overview from formation of tablet core to process control of parameter hardness

Results and discussions



Graph 1. Graphical display of parameter hardness of tablet cores for produced batch of the product

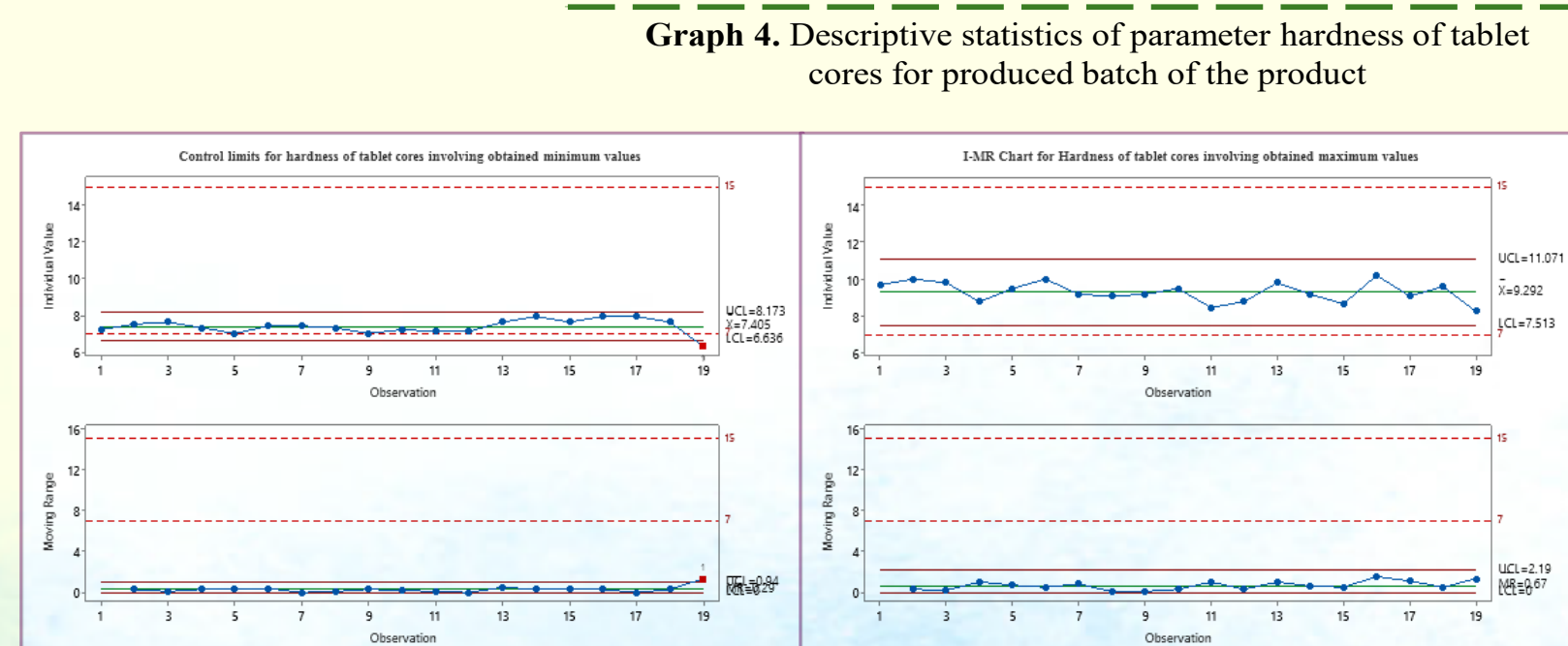


Graph 2. Process capability of parameter hardness of tablet cores for produced batch of the product

1. When calculating control limits including the obtained minimum values for the hardness of tablet cores, the need to redefine the specification limits for this product is observed.
2. When calculating the control limits including the maximum values obtained for hardness of tablet cores, it can be observed that the risk of recurrence of the deviation, but in the direction of values above the upper limit of specification, is eliminated. From the statistical evaluation it can be observed that values close to the upper limit of specification were not obtained for any of the produced batches.

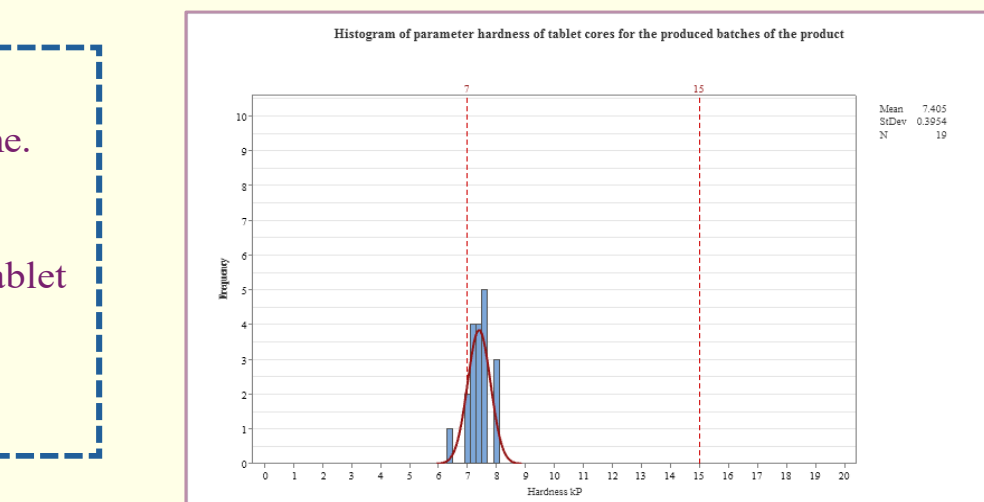
The parameter hardness of tablet cores in the batch under investigation is subject to deviation for the first time. In previously produced batches of the product, no deviations in the values for the parameter hardness were observed. Through the linear graph, it can be observed that the obtained minimum values for the parameter hardness of tablet cores for each of the batches processed in the statistical evaluation are trending towards the lower limit of specification.

Through Process Capability, processing the obtained minimum values, the value of 0,53 itself is below 1,33 and shows us that the process is not stable, is not well centered and that activities/measures need to be taken in order to establish a stable process.



Graph 3. Histogram of parameter hardness of tablet cores for produced batch of the product

Graph 5. Control limits of parameter hardness of tablet cores for produced batch of the product



Graph 4. Descriptive statistics of parameter hardness of tablet cores for produced batch of the product

The minimum values on the histogram show a tendency towards the lower limit of specification. Most of the batches are concentrated around the mean value, but one batch (frequency=1) is noticeable that is below the lower specification limit of 7kP (around 6,4kP).

Batch	Manufacturing Date	Minimum value for hardness of tablet cores kP	Maximum value for hardness of tablet cores kP	Average value for hardness of tablet cores kP
1	10.5.2019	7,24	9,68	8,46
2	10.5.2019	7,54	9,99	8,77
3	10.5.2019	7,65	9,79	8,72
6	27.1.2020	7,34	8,77	8,06
7	27.1.2020	7,03	9,48	8,26
8	27.1.2020	7,44	9,99	8,72
9	27.1.2020	7,44	9,17	8,31
10	4.5.2021	7,34	9,07	8,21
11	20.10.2022	7,03	9,17	8,1
12	20.10.2022	7,24	9,48	8,36
13	20.10.2022	7,14	8,46	7,8
14	15.2.2023	7,14	8,77	7,96
15	3.5.2024	7,65	9,79	8,72
16	3.5.2024	7,95	9,17	8,56
17	1.7.2025	7,65	8,66	8,16
18	1.7.2025	7,95	10,19	9,07
19	1.7.2025	7,95	9,07	8,51
20	9.10.2025	7,65	9,58	8,62
Specification limit		7 – 15 kP		

Table 1. Tabular display of parameter hardness of tablet cores for produced batch of the product

Conclusions

Statistical tools are crucial in the pharmaceutical industry because they enable the transition from assumptions to decisions based on real data. They are the most important tool in pharmaceutical production. By applying them, conclusions were reached regarding the product that was subject of the study.

Each of the tools used gave a realistic picture of the values for the hardness of tablet cores for the product.

According to the application of statistical tools, a conclusion was reached to redefine the specification limits of the parameter hardness of tablet cores with emphasis on the lower specification limit.

The application of histogram, line graph, descriptive statistics and process capability showed us the trend of values for the hardness of tablet cores close to the lower specification limit for each of the batches produced by the product.

The application of control charts defined the control limits according to the current specification limit, and is an auxiliary tool for proposing new redefined specification limits.