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Original Article

Measurement of Process Capability of Manufacturing Process of Levetiracetam by Applying Concept of Six Sigma

Chandni Chandarana*, Pratiksha Rai, Divya Jadhav

Department of Pharmaceutical Quality Assurance, SSR College of Pharmacy, Silvassa, UT of Dadra and Nagar Haveli, INDIA.

ABSTRACT

Background: A process capacity study is a study that uses capability indices to compare the output of an in-control process to specification constraints. Cp, Cpk, Ppk, and Pp are some of the statistics that can be used to assess process capability. The goal of the six-sigma study of levetiracetam tablets is to enhance and adjust the process to produce defect-free tablets and to maximize customer satisfaction. Process capability guarantees that procedures meet industry firm specifications while lowering process variation, which is essential for obtaining product quality characteristics. Before the batch is commercialized, this capacity research should be used in the industry. It is a cost-effective strategy that can shorten the inspection process. **Materials and Methods:** The control and capabilities of Antiepileptic tablets are described in this study. The research focuses on data collecting and analysis of process capability utilizing statistical software such as MINITAB 19.1. **Results:** The results of process capabilities for all the processes like hardness test, thickness test, disintegration test, loss on drying and friability tests were found to be above 1.33. **Conclusion:** The existing capability of the process is judged to be capable in this research.

Keywords: DMAIC phases, Epilepsy disorder, Levetiracetam, Process capability index, Six sigma process.

Correspondence:
Dr. Chandni Chandarana
Assistant Professor, Department of Pharmaceutical Quality Assurance, SSR College of Pharmacy, Silvassa-396230, UT of Dadra and Nagar Haveli, INDIA.
Email: chandnichandarana7343@gmail.com

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INTRODUCTION

Six Sigma is a quality and management tool for problem solving methodology to improve the key process (Figure 1).[1] It is a business process which eliminates product defects. It is a disciplined based approach for reducing product and process variation.[2] Six Sigma describes the performance of a process quantitatively using statistical approaches. Six sigma includes financial results that are monitored and reported, enhanced data analysis tools, project management tools, and an emphasis on customer service and methods.[3]

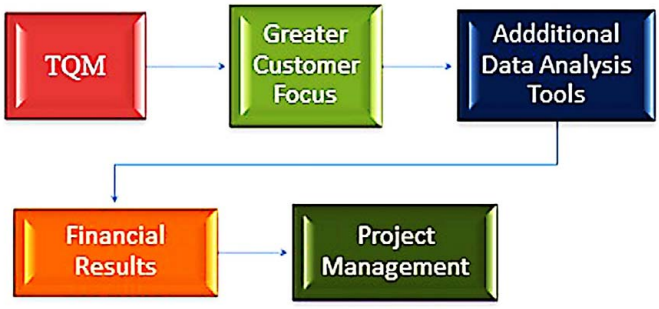

Figure 1: Process of six sigma.[1]

In the 19th century, German mathematician and scientist Carl Fredrich Gauss devised the bell curve, which became a tool for detecting faults and defects in the Six Sigma process. Bill Smith, a Motorola engineer, created the six sigma concepts in the mid-1980s. Motorola engineer faced a huge loss on share market, and he measured defects in thousands of products. So, Motorola established Sigma concept which gave a tremendous success in business performance by improving quality, reducing costs, eliminating defects and increasing the markets for products and services. Other companies like Samsung electronics, Dupont and Honeywell have also used to adopt this methodology.[4,5]

DMAIC Approach in Six Sigma[6,7]

The DMAIC model is a cycle that uses five basic processes to eliminate defects or improve opportunities in the process for business improvements: define, measure, analyses, improve, and control (Figure 2).

Define

The first step in the DMAIC technique is to define. It specifies the CTQ (critical to quality) issues as well as the central business process.

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Measure

This is the DMAIC's second stage. Data is gathered from many sources in order to determine the sorts of problems and metrics. It entails gathering data, defining the unit, identifying opportunities and flaws, determining process capability, and validating the process system.

Analyze

It includes identification of sources of variation, determination of root causes and prioritizing the root causes.

Improve

Eliminating and controlling the causes for achieving the required breakthrough performance. It includes generating alternative solution, designing the solution and proving the effectiveness of the solution.

Control

This is the last phase of DMAIC in which we ensure the improvements made in improve phase and that the problems does not reoccur.

Process capability index (Cpk)

is a statistical method for estimating a process' ability to produce output within the customer's specified constraints

$$Cpk = \text{Minimum of } [\bar{x} - LSL/3\sigma, USL - \bar{x}/3\sigma]$$

Process capability (Cp)

It is defined as the comparison of the Voice of the Customer. It is used to quantify information which tells you as to whether fulfilling the customer expectations. Cp values are equal to 1, greater than 1.33.

$$Cp = USL\text{-}LSL/6s$$

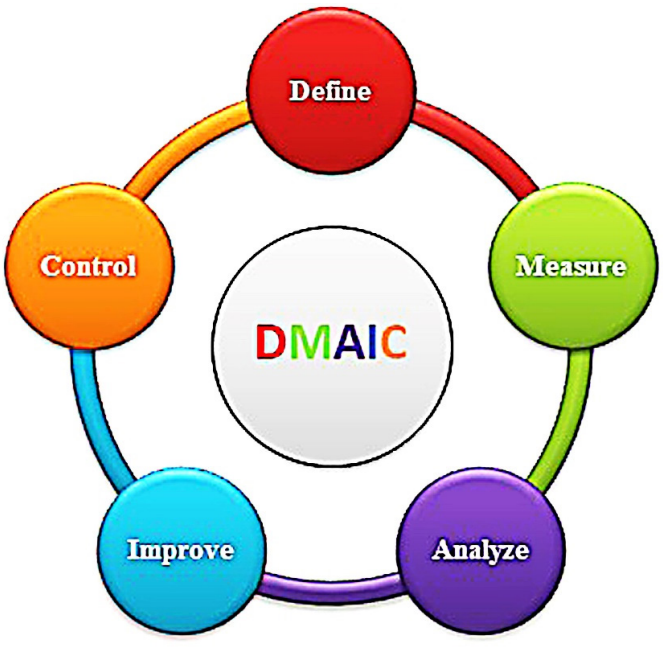

Figure 2: DMAIC cycle.[7]

Performance Index (Pp)

It calculates how effectively the data is placed inside the specified parameters (USL, LSL). If the process is centred between the limitations, it is only implicated if it would be put if it was cantered

$$Pp = (USL - SL)/6\sigma$$

Process Performance Index (Ppk)

It determines how effectively the system meets the specifications and also ensures that the process stays within the specified parameters. It calculates process performance in terms of dispersion and centeredness.

$$Ppk = \min \{USL - \mu/3\sigma \text{ overall}, \mu - LSL/3\sigma \text{ overall}\}$$

Epilepsy Disorder[8]

Epilepsy is a brain illness that causes unprovoked seizures in people of all ages, with a special preference for children and the elderly. Along with seizures, many individuals experience cognitive and psychological issues as a result of the seizures and their treatment.

There are various different types of seizures that a person can have

1. Epilepsy (generalised).
2. Epilepsy with a single focus.
3. Epilepsy with both generalised and focal features.
4. Unidentified epilepsy.

Levetiracetam Tablet[9,10]

Levetiracetam is a novel anticonvulsant drug that is used as a supplement to treat partial onset, myoclonic, and generalized tonic-clonic seizures in epilepsy patients. (S)-2-(2-oxopyrrolidin-1-yl) butanamide is its chemical name (Figure 3).

Levetiracetam's effect is dependent on its ability to bind to synaptic vesicle protein 2A (SV2A). The membrane-bound protein SV2A is found on synaptic vesicles and is found throughout the CNS. Levetiracetam may limit neurotransmitter release by stimulating presynaptic SV2A, however this activity does not appear to disrupt normal neurotransmission. As a result, it's been proposed that levetiracetam only modifies SV2A function in pathological conditions.

Literature survey revealed that there was no analytical method for measurement of the process capability of six sigma on levetiracetam tablet. This revealed that there was an analytical

method to measure process capability of six sigma on various drugs like Ranitidine,[11] Antihypertensive tablet,[12] Baclofen-Orally Disintegrating Tablets (ODTs),[13] Oral Solid Dosage Case Study,[14] Metformin Hydrochloride,[15] Cefdinir and Sodium Benzoate,[16] Omeprazole Capsules,[17] Amlodipine Tablet,[18] Ibuprofen Tablet.[19]

MATERIALS AND METHODS

Materials

Name of software

Minitab 19.1(32-bits) software used in process capability. Levetiracetam tablet was collected from Sun Pharmaceutical Industries Limited, Pipariya, Silvassa.

Methods

Various process parameters are involved in the production of tablet were as follows:[20-23]

Hardness test

Using a Monsanto tablet hardness tester, the crushing strength Kg/cm^2 of produced tablets was assessed for thirty tablets from each batch. The standard deviation and average hardness were calculated.

Disintegration test

A Disintegration Apparatus USP standard was used to disintegrate six tablets from each batch in distilled water at 37°C. The disintegration time was defined as the time during which no granule of any tablet was remained on the apparatus mesh.

Friability test

Take a sample of complete tablets for tablets with an average weight of 0.65 g or less. Take a sample of 10 entire tablets for tablets with an average weight of more than 0.65 g. Dedusted the tablets with care and weighed them precisely. The pills were inserted into the drum and spun 100 times. The tablets have been removed, any dust has been removed, and the tablets have been correctly weighed. The percentage friability was measured using the formula,

$$\% F = \{1 (Wt/W)\} \times 100$$

where, % F= friability in percentage W= Initial weight of tablet Wt= Weight of tablets after revolution.

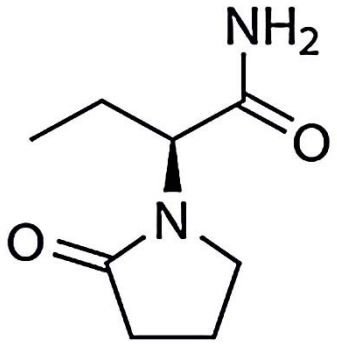

Figure 3: Chemical structure of Leviteracitam.[10]

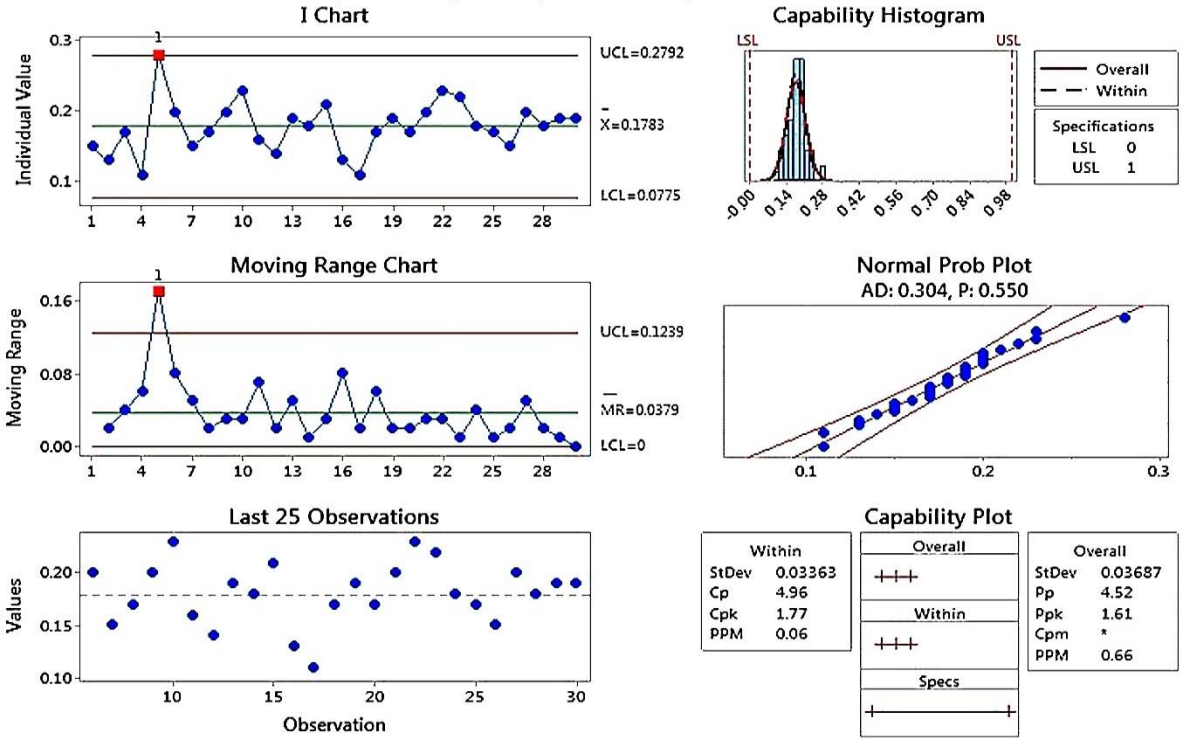

Figure 4: Process capability report of friability test.

Table 1: Observations of process parameters.

Sample number	Hardness test (kp)	Thickness test (mm)	Disintegration test (min)	Friability test (%)	Loss on Drying (%)
1	13.0	7.01	3 min 49 sec	0.15%	0.62%
2	14.4	7.13	3 min 42 sec	0.13%	0.75%
3	14.4	7.11	3 min 47sec	0.17%	0.98%
4	14.0	7.12	3 min 35 sec	0.11%	0.86%
5	13.9	6.99	3 min 39 sec	0.28%	0.78%
6	12.6	7.10	3 min 42 sec	0.20%	0.99%
7	13.6	6.99	3 min 40 sec	0.15%	1.0%
8	13.4	7.13	3 min 35 sec	0.17%	0.68%
9	12.9	7.01	3 min 42 sec	0.20%	0.77%
10	12.8	6.97	3 min 30 sec	0.23%	0.65%
11	14.5	7.04	4 min 50 sec	0.16%	0.68%
12	14.0	7.10	4 min 12 sec	0.14%	0.75%
13	13.8	7.01	4 min 00 sec	0.19%	0.81%
14	14.6	7.11	3 min 38 sec	0.18%	0.83%
15	13.7	7.01	3 min 44 sec	0.21%	0.74%
16	13.4	7.08	4 min 30 sec	0.13%	0.61%
17	14.7	7.09	4 min 20 sec	0.11%	0.69%
18	12.9	6.98	3 min 50 sec	0.17%	0.74%
19	12.4	7.12	3 min 37 sec	0.19%	0.73%
20	12.6	7.15	3 min 44 sec	0.17%	0.73%
21	12.9	7.10	3 min 53 sec	0.20%	0.88%
22	13.4	7.10	4 min 18 sec	0.23%	0.86%
23	13.3	6.98	4 min 23 sec	0.22%	0.71%
24	12.7	7.08	4 min 17 sec	0.18%	0.70%
25	13.7	7.10	4 min 40 sec	0.17%	0.73%
26	12.4	7.06	4 min 35 sec	0.15%	0.78%
27	12.3	7.02	3 min 57 sec	0.20%	0.83%
28	13.1	7.04	3 min 53 sec	0.18%	0.69%
29	13.2	7.02	4 min 00 sec	0.19%	0.65%
30	13.4	7.08	4 min 07 sec	0.19%	0.79%

Thickness test

Thirty tablets were chosen at random from each batch and measured using a Digital Vernier Caliper.

Loss on Drying

Weighed the sample accurately and placed roughly 2-5 g in a previously dry and tared flat weighing vial. The sample was dried in an oven at 100-105°C or in desiccators over phosphorus pentoxide at ambient temperature and atmospheric pressure. Dry the sample until the difference between two successive weighing is less than 5 mg.

RESULTS AND DISCUSSION

The observations of performed study is described in Table 1. For friability analysis, the process capability was found to be 4.96, cpk was found to be 1.77, pp was found to be 4.52 and ppk was found to be 1.61 (Figure 4). For disintegration analysis, process capability was found to be 10.46, Cpk was found to be 4.10, pp was found to be 5.79 and Ppk was found to be 2. (Figure 5). For Hardness test analysis, process capability was found to be 3.59, cpk was found to be 0.96, pp was found to be 2.87 and ppk was found to be 0.77 (Figure 6). For Loss on Drying test analysis, process capability was found to be 2.49, cpk was found to be 1.80, pp was found to be 1.95 and pp. was found to be 1.41 (Figure 7). For Thickness test analysis, process capability was found to be 1.60, Cpk was found to be 0.74, pp was found to be 1.85 and ppk was found to be 0.86 (Figure 8). For process capability, results were found to be above 1.33 for all analysed parameters, so all process are capable.

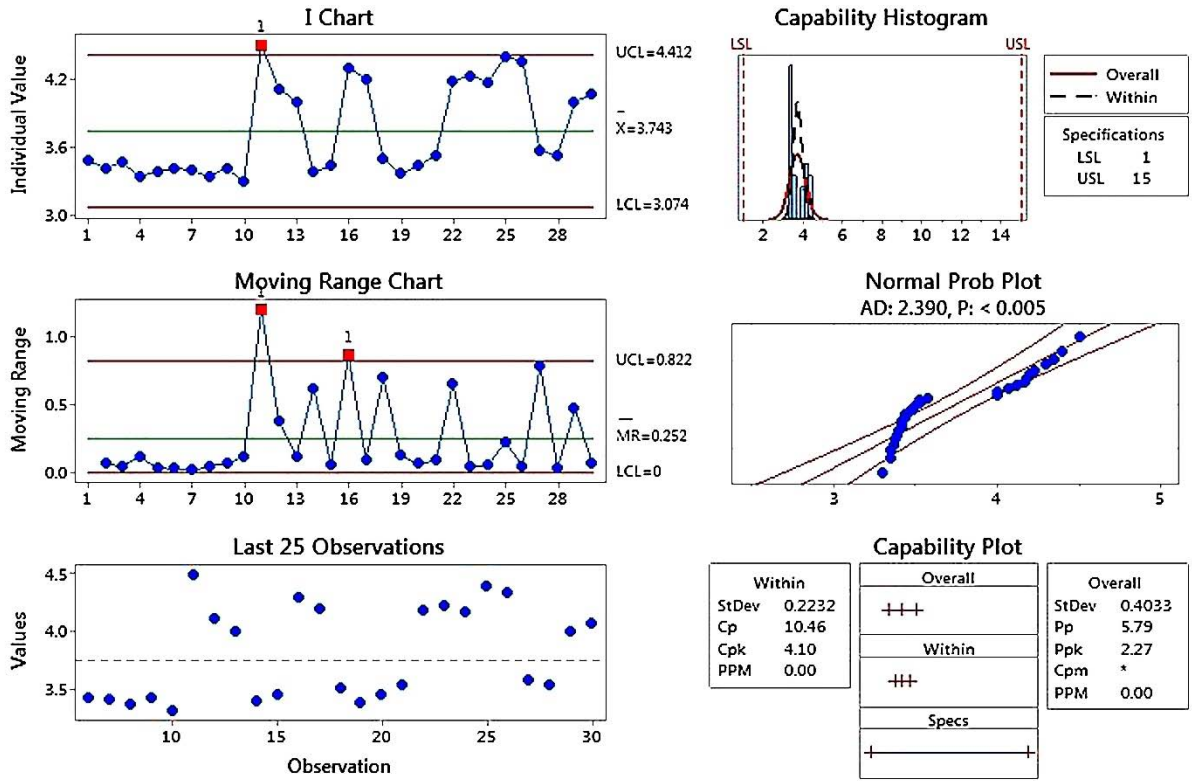

Figure 5: Process capability report of disintegration test.

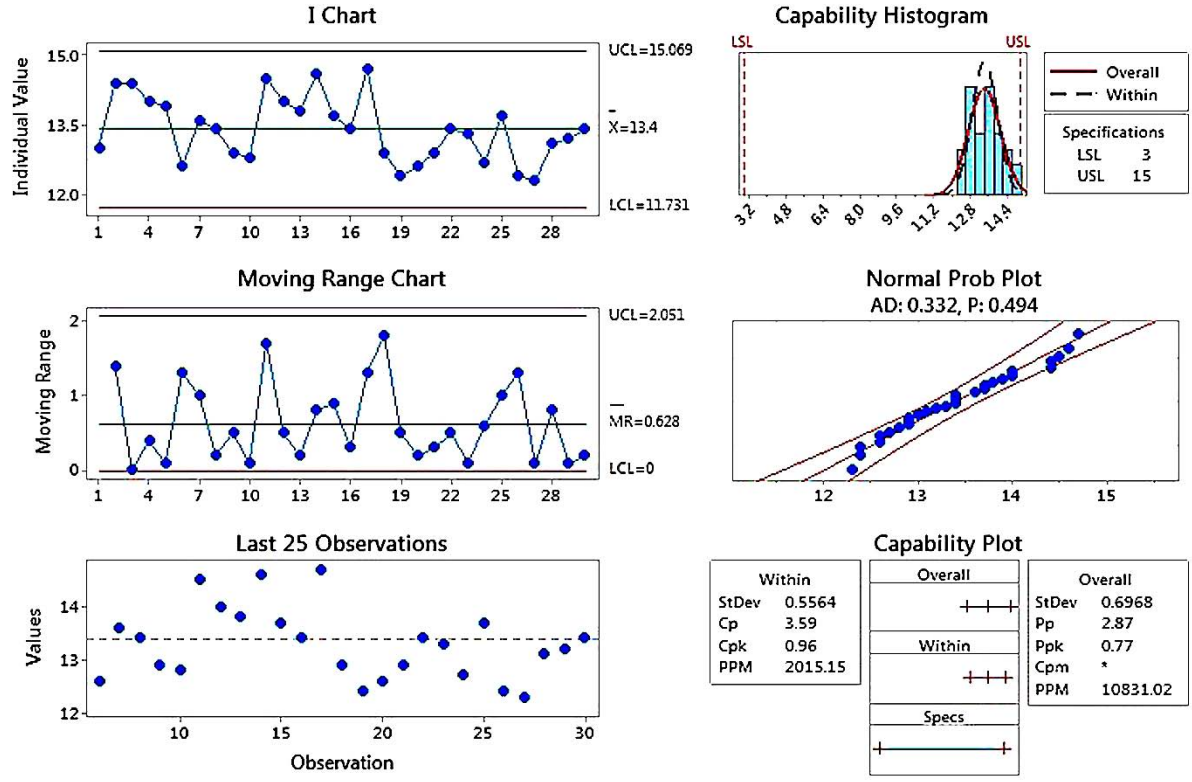

Figure 6: Process capability report of hardness test.

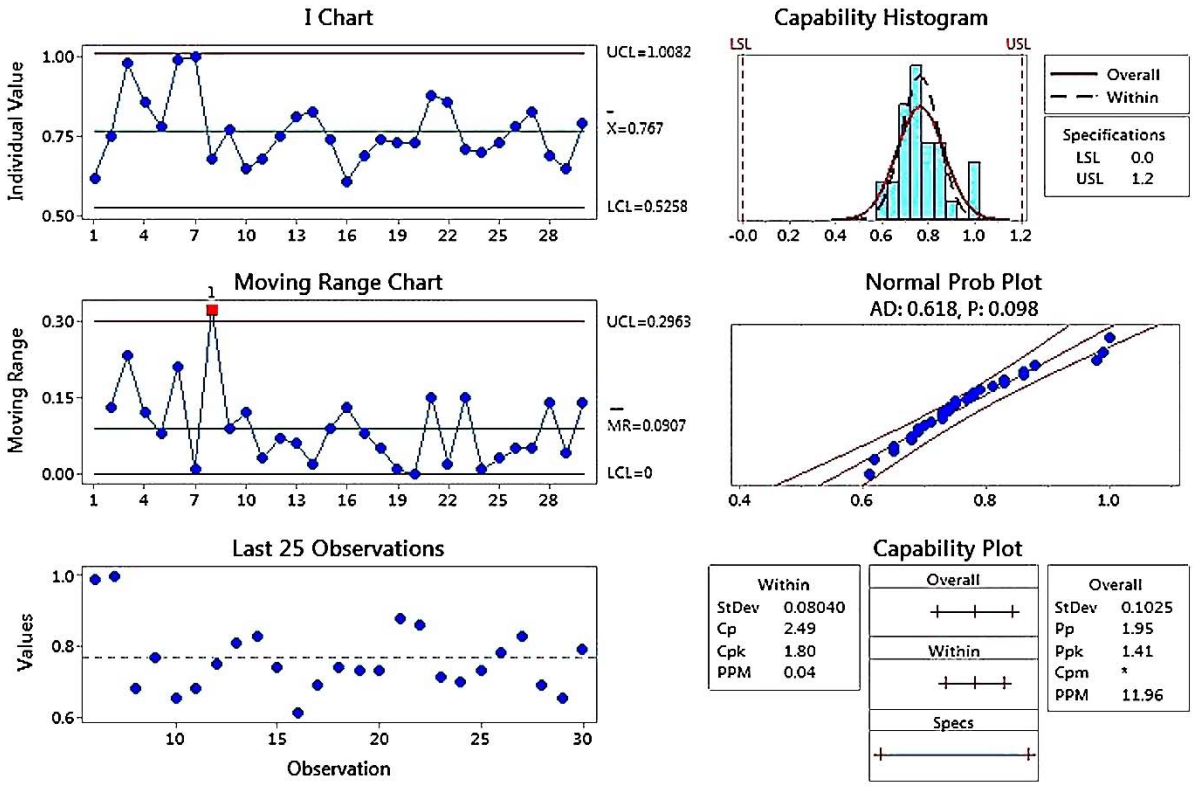

Figure 7: Process capability report of loss on drying test.

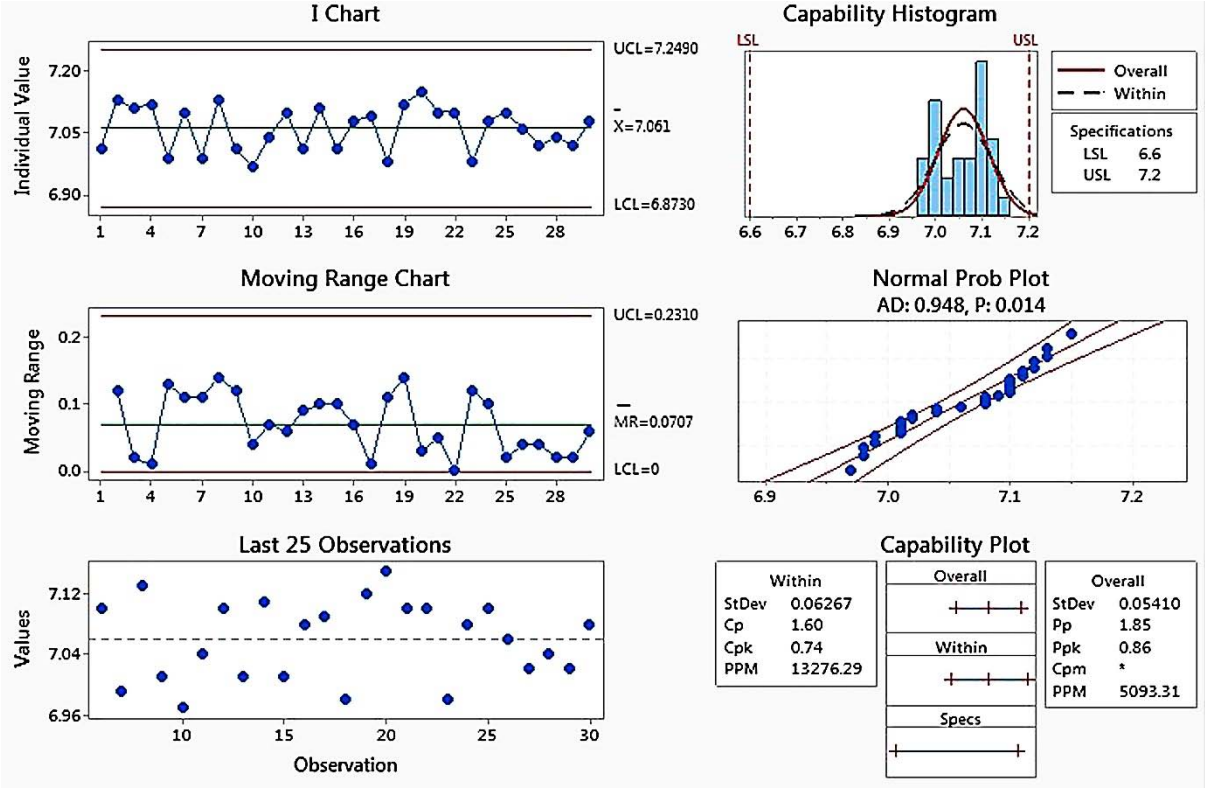

Figure 8: Process capability report of thickness test.

CONCLUSION

With 30 tablets, the study was conducted to check the parameters like hardness, thickness, loss on drying, disintegration, and friability tests. The necessary control charts were displayed in six sigma, and the results were analyzed, as well as data capability indices at specification limits. The study was performed in Minitab software 19.1 and from results, it can be stated that the process was under control and capable of producing high-quality products.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

Cp: Process capability; **Cpk:** Process capability index; **CPM:** Capability index; **DMAIC:** Define, Measure, Analyze, Improve, Control; **Pp:** Performance index; **Ppk:** Process Performance Index; **PPM:** Parts Per Million Defectives.

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