

Recent trends in process capability in the pharmaceutical industry

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Abstract

Pharmaceutical industries are among of the largest companies. The aim of manufacturers is to produce free of defects products and make them available for consumers. A number of process monitoring and control strategies have been developed to produce quality products. Process capability indices have increased in use and variety. It is a statistical approach to inherent process variability. For this purpose, a systematic review was performed and findings were summarized. Studies have demonstrated that process capability study has improved the manufacturing process in the pharmaceutical industry. Various methods such as computing Cp and Cpk values, and applying DMAIC approach are being widely used by manufacturers to produce quality products. Process capability as a tool has been powerful enough to affirm the quality of the produced dosage form. Findings revealed that by minimizing variations, manufacturers can make processes fit for the industry and produce quality products. Literature has suggested that the industry should

conduct capability studies prior to commercializing the manufactured batch.

Keywords

Process capability, Process variation, DMAIC approach, Product quality, Process improvement

1. INTRODUCTION

Pharmaceutical industries are among of the largest companies. It impacts human health and the welfare of society. The aim of manufacturers is to produce free of defects products and make them available for consumers. Similarly, consumers look for products that are of good quality and serve the desired effect. This industry spends a lot of time and resources on the research and development of new drugs. This results in increased competitiveness within the industry to accomplish the goal of serving humanity. Additionally, the demand for quality products has been raised. (Md Abubakar, 2020).

According to the International Conference of Harmonization ICH Guidelines Q8, “Quality cannot be tested into products i.e., quality should be built in by design”. The pharmaceutical quality testing system focuses on ensuring quality in products by testing raw materials, including active pharmaceutical ingredients (API) and excipients, dosage form manufacturing, the process of manufacturing, in-process testing of materials, and finished product testing. Not only the drug substances but the process needs to be monitored closely. (Amit S. Patil, 2013). This Quality by Design (QbD) concept was proposed by Joseph Moses Juran in 1985. He explained that quality-related problems arise from the way it was planned. (Sangshetti, Deshpande, Zaheer, Shinde, & Arote, 2017).

A number of process monitoring and control strategies have been developed. These are designed with the intention to produce quality products. These are optimized during production to ensure end-product quality. It is important for the evaluation of the quality of the drug's substance at release and testing of the drug prior to its commercialization (Qinglin Su, 2019). In the case

of an oral solid dosage form, there are multiple factors that affect the quality of the finished product, such as raw materials and anything that disturbs the process (Ravendra Singh, 2015).

Process robustness is directly related to the defect in the product. For a process to be robust, it should demonstrate acceptable performance and product quality and be able to tolerate variability in inputs simultaneously (Chowdhury, 2013). To ensure the reproducibility of a process, a capability study is a prerequisite.

Process capability indices have increased in use and variety. Their use has made improvements in process and ultimately increase product quality (Johnson, 1993). It is a statistical approach to inherent process variability. It is aimed to identify inappropriate specification limits and identify variability in the process. Also, process capability indices assist manufacturers in taking necessary corrective actions when required. The process capability index is the value of tolerance specified for a particular characteristic divided by a standard deviation (Chabukswar *et al.*, 2011; Goswami & Dutta, 2013; Vugigi, Mshila, & Ogaji, 2021).

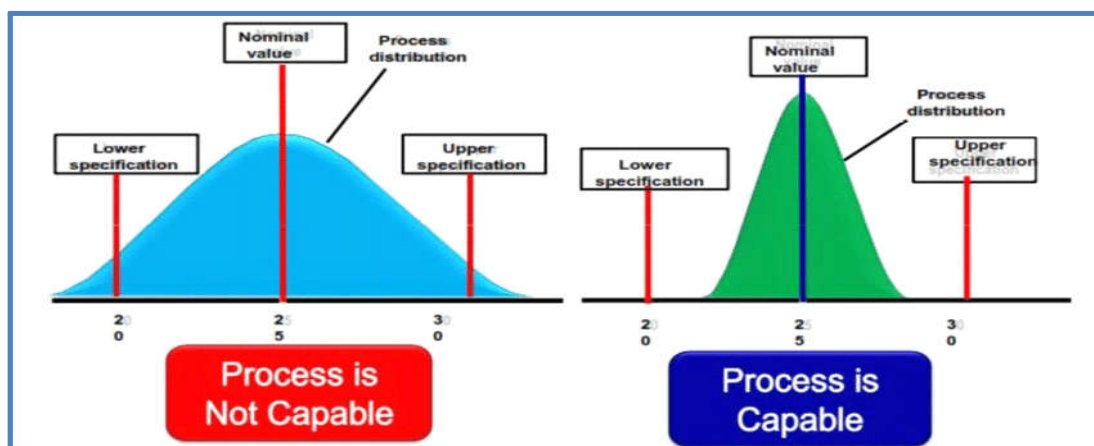


Fig- 1: Capability of a process based on spread of process distribution across the specification (Prabhakaran, 2020).

The formula can be expressed as:

Process Capability Index (Cp):

Upper Specification of Limit - Lower Specification of Limit / 6 Standard Division

Table no 1: Significance of different values of Cp (Mahapatra *et al.*, 2020)

Cp= (USL-LSL)/6 sigma		
Cp<1	The process is not capable	The process variation exceeds specification, and a significant number of defects are being made.
Cp= 1 to 1.33	A barely capable process	The process is just meeting specifications. A minimum of 3% defects will be made and more if the process is not centered.
Cp> 1	The process is not capable	The process variation is less than the specification; however, defects might be made if the process is not centered on the target value.
Cp> 1.33	A highly capable process	This process will produce conforming products as long as it remains in statistical control. The process owner can claim that the customer should experience least difficulty and greater reliability with this product. This should translate into higher profits.

Another process capability index is Cpk. Cpk is widely used to estimate what the process is capable of producing. It evaluates the process spread while considering that the mean might not be centered with specification limits. If the process variation is located within specification limits then calculated values for Cpk will be equal to that of Cp. However, as the process variation begins to move out of the specification, it is evaluated that how far it lies out of limits. A value of 1.33 for Cpk shows that the process is capable. If the value is lesser than 1.33, it can be assumed that either process variation is excessively wide or variation is offset from the center. (Wooluru, Swamy, & Nagesh, 2014).

The equation can be derived as:

$$CpK = \min \left\{ \frac{USL - \hat{\mu}}{3\sigma}, \frac{\hat{\mu} - LSL}{3\sigma} \right\}$$

Where $\hat{\mu}$ is the estimated mean. USL is the upper specification limit and LSL is the lower specification limit.

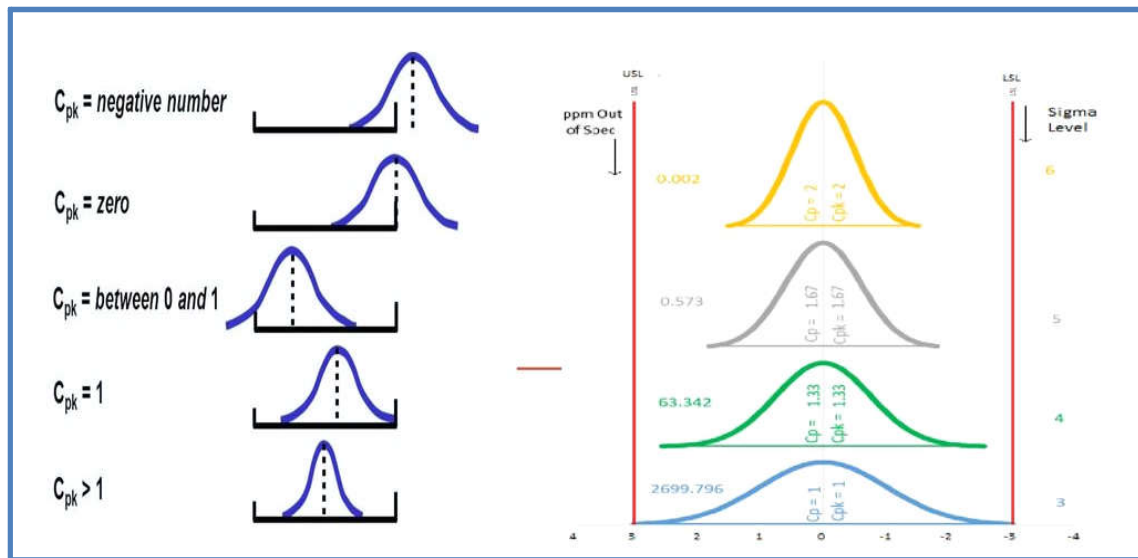


Fig-2: Cpk with respect to distribution of mean- extracted from (Karale, 2019)

In general, process capability analysis can be understood as a comparison between the Voice of Customer (VOC) and Voice of Process (VOP). (Haleem, Salem, Fatahallah, & Abdelfattah, 2015).

Statistical Process Control (SPC) is a concept given by Dr. Walter Schewart. According to it, a process that shows special variation causes is considered as unstable and unpredictable. For this, control chart is a specific tool that is applied to represent descriptive statistics graphically. (Patel, Desai, & Thaker, 2015).

Another used method used in DMAIC or Six Sigma. Six Sigma operates a distinctive system of measurement, designed procedures, and devices. It is a mostly applied problem-solving approach to address quality problems and improve processes. Literature has expressed that carrying out six sigma study during the process can empower organizations to improve process and other operations (Rimantho, Hernadi, Cahyadi,

Prasetyani, & Kurniawan, 2017). Six sigma approach has benefited pharmaceutical industry by reducing rejects reworks of manufactured batch. (Antony, Gijo, Kumar, & Ghadge, 2016).

A trendy methodology uses a five-step fixing tool called DMAIC.

The DMAIC apparatus cabinet stands for define, measure, analyze, improve, and control.

I. Define:

It is the initial phase in which the problem statement should be well-defined. Necessary background information about the problem should be defined. Adding to this, it should be mentioned that what tasks are need to be accomplished, which team members are to be involved and other details such as cost and materials involved. Certain tools such as Pareto Chart, brainstorming etc. can be employed in this phase. (M. Prabhakaran, 2020).

II. Measure:

Measurement of critical process parameters (CPP) should be done to check whether it is under or out of specifications. It is a necessary step to undertake because it directs the problem solvers towards the root of the problem and solutions (M. Prabhakaran, 2020).

III. Analyze:

Analysis of variability in the process should be done and a possible steps to be undertaken

undertaken should be decided. It highlights the main rootcause that underlies the problem. This can be performed by constructing a fish bone diagram, which was designed by Kaoro Ishikawa. It is one of the basic quality tools and it is also known as Ishikawa diagram. Statistical tool like ANOVA (Analysis of Variance) is mostly applied to know which factor is crucial (M. Prabhakaran, 2020).

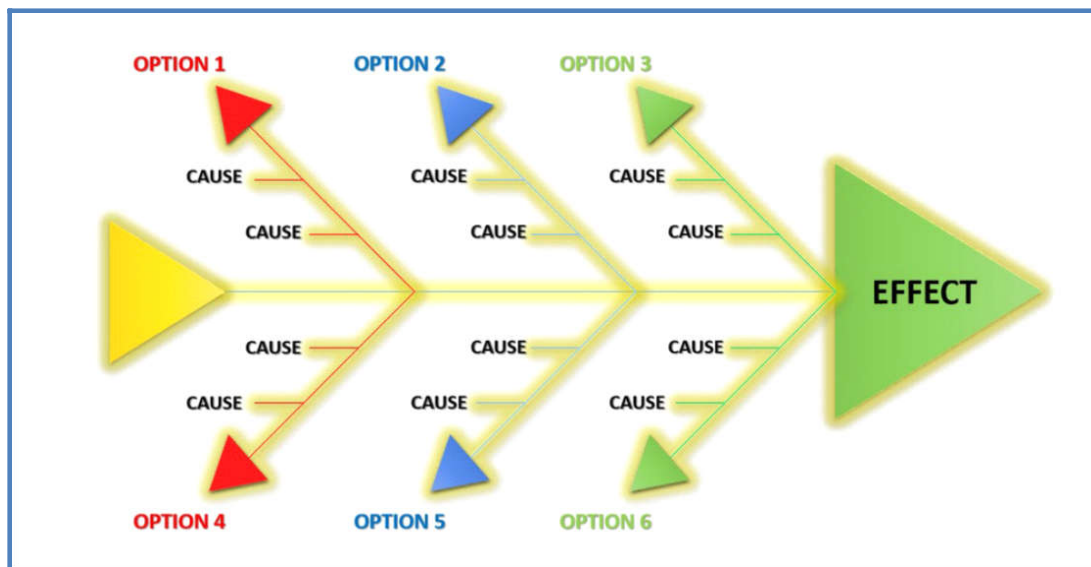


Fig-3: Fish bone diagram- Extracted from (Kajal, 2016)

IV. Improve:

In order to the reduce the recurrence of problems in a process, corrective actions should be incor- porated and the process should be redesigned. Application of scientific tools and graphs can help improve process capability and produce quality products of customer acceptability (Amanah Pasaribu, 2018; M. Prabhakaran, 2020).

Literature suggests a 5W and 1H method

which is explained as follows:

1. What the action for improvement is needed?
2. Where is the area for improvement to take place?
3. Why there is a need to do improvements?
4. Who will be responsible to carry out improvement actions?
5. When will the improvement action take place?
6. How will the improvement action take place?

V. Control:

The incorporated measures should be evaluated and results should be monitored and documented properly. This phase involves the standardization of improvements made in the process to achieve sustainable achievements.

For this purpose, control charts can be developed to comprise process settings, and procedures. It will assist the employees to follow specific details and requirements in performing daily tasks (M. Prabhakaran, 2020).

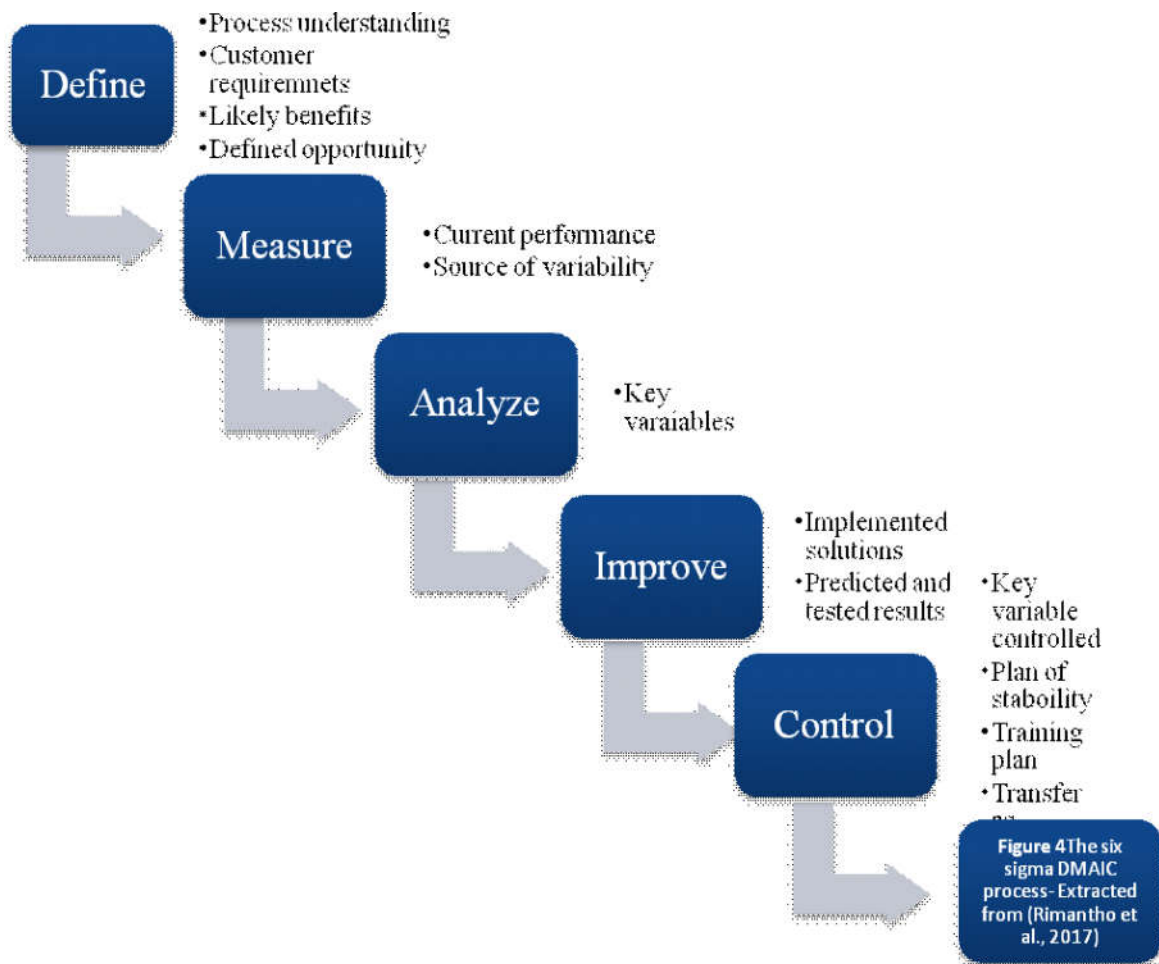


Fig- 4: The six sigma DMAIC process- Extracted from (Rimantho *et al.*, 2017)

3. MATERIALS AND METHODS

A Review on the topic of “Recent Trends in Process Capability in Tablet Manufacturing” was conducted from the literature published in last ten years from January 2012 to December 2022. Google scholar and research gate were the databases used for collecting the published literature related. More than 40 articles were downloaded from these databases. Abstracts were reviewed of downloaded articles. 12 articles were rejected after careful review of Abstract. After this screening a detailed review was done for the remaining articles. Results were evaluated and tabulated, compared with publications of different authors and conclusions were made.

4. RESULTS AND DISCUSSION

The process capability study was performed on the cofta tablets manufacturing process. Two main characteristics, such as weight and thickness, were considered. Specification limits were set: 950-1050mg and 3.57 to 3.97mm respectively. Results showed that Cp value for weight was 1.29 while Cpk value was 1.17. It indicated that the process was capable for weight. However, for thickness, Cp and Cpk values were 0.51 and 0.41 respectively. This showed that the process was not capable for thickness. Depending on the results, the manufacturer is recommended to make adjustments in specification limits for both weight and thickness (Adekeye, 2013).

One of the most well-known methodologies is Lean Six Sigma, which includes a variety of integrated tools like process mapping, value stream mapping, cause-and-effect matrices, and failure mode and effect analyses. In this study, the DMAIC methods of Lean Six Sigma were used to identify one of the chosen production

used to identify one of the chosen production regions. (Ismail, Ghani, Ab Rahman, Md Deros, & Che Haron, 2014).

The study reviewed three major in process control variables which were tablet hardness, thickness and weight. Process capability studies were conducted, which showed a Cpk value of 1.61. It demonstrated that the process is robust. For the weight variation test, 20 tablets were weighed. The specification range was 100 ± 2 mg per tablet. The results showed process is in control. Tablet thickness was found out to be in control while manufacturing to ensure proper packaging (Taherian & Asl, 2016).

The study applied that the method of lean Six Sigma and waste management with the aim to reduce use of organic solvent from the analytical method. A reverse phase liquid chromatographic method was developed to estimate Ranitidine HCl for tablet dosage form. By applying DMAIC principles, it was evaluated that method had improved process capability (Nikhil Belamkar, 2016).

Application of lean Six Sigma and other quality tools played an important role in assessing process changes and variability. Data for last two years was collected from different suppliers. Process capability analysis identified that between the two suppliers one is statistically capable and was found accurate than the other. The Cpk was calculated as 1.83 (Hassouna & Mohamed, 2019).

A case study has highlighted that a pharmaceutical company applied Six Sigma strategy to reduce tablet defects and improve quality in the year 2017. The research data were collected and analyzed. Results indicated that tablet defects were 0.27%, which exceeded the allowed tolerance of defects i.e., 0.10% of

the total production. By using a Pareto chart, it was evaluated that the most common defects were spot drug tablets, tablet mottling, collapsed and peeled off. Root- cause analysis was then carried out to find out the underlying causes of the mentioned defects. Improvements were made in the process to reduce the occurrence of defects. The study concluded that by applying the DMAIC approach reject rate was dropped down to 0.0081% with a sigma level of 5.45% (Winatie, Saroso, Purba, & Wirani, 2020).

The main objective of this review analysis was to discuss the trends regarding process capability and to highlight its significance in tablet production.

Process validation and contents uniformity study were conducted on tablets manufactured in batches at the Industrial Lab of Faculty of Pharmacy, Hamdard University, Karachi. A total three batches were produced and sampled. Quality tools and process capability analysis were performed on the samples. The histogram plot showed that the data did not have any upward and downward trends and no evidence of non-randomness. Cpk value was computed as 1.206 for all batches. However, the desired Cpk value was 1.33. Conclusions were made that the process was leading towards capability. Also, it was predicted that the process would meet the specifications of content uniformity. This literature suggested that, the study is beneficial for the pharmaceutical industry if they are streamlining their process (SohailAnwer, 2014).

Rahul Raj *et al* conducted a process capability study on the production of antihypertensive tablets (10 mg). Various statistical control tools were applied along with Minitab-16 software. The study was performed on weight variation

of 25 batches of tablets. The results shows that no statistically significant variations were observed in the sampled batches. The process stood capable due to changes in selection of critical parameters, collection of data, process capability study and data evaluation. It also revealed that by minimizing variations, we can make processes fit for industrial use and producing quality products. The study suggested that industry should conduct capability studies prior commercialization of manufactured batch. (Rahul Raj S, 2017).

Chopra *et al* used sigma process capability to find out the tablet production process quality. Basic statistical tools lower the diversity of procedure which lessens the product performance. Statistical Process Control (SPC) has been declared as a tool for regular and nonstop development of quality. For this SPC study, Acyclovir 30 mg tablets were made by wet granulation method. Eminent Critical quality attributes (CQA), like: assay, mass uniformity, dissolution and water-content were sorted out, using Failure Mode Effect Analysis (FMEA) and data were gathered. Statistical tools were applied, data was brought together and interpreted using the SPC tool. Minitab statistical software was used for the creation of control and capability charts. This study was concluded as the selected process of tablet manufacturing was stable and followed 4 sigma capability. Pareto charts illustrated that the dissolution process was varied the most and was least capable. So, for achieving a 6 sigma capability, dissolution needed a breakthrough, leading to continual quality improvement (Chopra, Bairagi, Trivedi, & Nagar, 2012).

Fischer *et al*. In a quality improvement research, known to be one of the largest sampling study, samples of 252 Immediate-release solid oral drug products were taken. These difficult-to-

make medicines were tested by FDA on the foundation of their quality history issues. Although the FDA samples pharmaceutical products regularly, special consideration was given to them as they were manufactured for the US market but in US, Canada, Europe, India and rest of Asia. FDA had been keeping a check on these unbranded drugs from all countries, anywhere in the world. 73% of health care practitioners (HCP) had claimed to prescribe as-written brands to avoid brand substitution, on users request as well. The data presented in the study have enlightened major quality attributes: content uniformity and dissolution. They were used to calculate Process Performance Index (Ppk) to indicate variability in their production. As the outcome of statistical analysis, regarding content uniformity, Ppk of all samples was 1.73, that is, exceeding 5-sigma capability. On the contrary, variability in dissolution performance in some countries was less, however; branded drugs had a higher Ppk for dissolution inspite of the fact that even the unbranded drugs met the US Pharmacopeial limit (Fisher *et al.*, 2020).

Eissa *et al.* demonstrated stability and controlled variation within the normal range with respect to time. If the production steps had been followed properly. For this purpose, Control charts were quite capable to identify and pointing out variability in the process due to normal process fluctuations. This study investigated the quality of pharmaceutical product batches via monitoring assay results and trends retrospectively. Manufacturing of the product was carried out in a pharmaceutical firm's QC laboratory and assayed (relative potency check as claimed dose per tablet). The active components involved were

Acetaminophen, Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride. Comparison of performance and trend of the batches was accomplished using Individual-Moving Range and Laney U' chart. Box-and-Whisker diagram illustrated that relative potency of Chlorpheniramine Maleate was significantly higher than that of Acetaminophen and Pseudoephedrine Hydrochloride. Laney U' and I-MR charts had the same control limits, but the latter was more sensitive in detecting out-of-control states. On the other hand, Laney U' chart was interpreted easily, without the need of special prerequisites before its application. Both types of charts were on the same line in terms of control limits, that is, upper control limit (UCL) and lower control limit (LCL). SPC tools were helpful to figure out the non-consistency in the production batches, requiring further investigation (Eissa, 2018).

Al. Refaie *et al.*, applied Six-Sigma approach, DMAIC and grey relational analysis to enhance the process of direct compression with the weight and hardness of tablets. The process was found capable for hardness but incapable for weight. DMAIC methodology was acquired to upgrade the performance of this process. The speed of the machine, compression force and filling depth were the main factors considered. The Taguchi's L27 array was adopted to investigate the effects of these three process factors contemporaneously. Then, the grey relational analysis based on the grey system theory was utilized for solving complicated interrelationships among multiple quality responses and to determine the combination of optimal factor levels. In the start, the Cpk value for hardness was improved from 1.5 to 3.31. While, the Cpk value for weight was enhanced from 0.587 to 0.848. Furthermore, the MCpk index (to

be used as a capability measure for a process having multiple performance measures) was improved from 0.938 to 1.68, which indicates great savings in manufacturing and quality costs. Confirmation experiments were conducted and attained improvement was shown. In conclusion, DMAIC approach, including grey relational analysis, proved effective for improving the performance of direct compression with the weight and hardness of tablets (Al-Refaie, Li, Jalham, Bata, & Al-Hmaideen, 2013).

Bhavin *et al.* adopted Six Sigma methodology which has enabled the pharmaceutical industries to reduce waste and improve routine manufacturing processes. It saves time that is spent in end product testing. The manufacturer can predict and eliminate potential errors in process and defects in the product by applying following DMAIC methodology (Bhavin D. Pandya, 2022).

Cadinoska *et al.* A system approach, TIPS and TRAPS, helped users to develop an effective process monitoring system, avoiding errors. Design and implementation of this approach Use of control charts has been a necessary tool when it comes to data analysis of critical quality attributes, and detecting underlying reasons of variability of the process. They can provide adequate knowledge about routine operations and processes. Critical data can be monitored efficiently that results in developing prompt response to eliminate variations and defects (Cadinoska *et al.*, 2019).

Bermejo *et al.* presented some recent advances in Process monitoring, control and improvement. Process monitoring provides the tools for enabling CPV and dealing with variation. The requirement to understand, ability to detect, understand the impact and ability to control variation has been clearly stated in FDA guidance.

Process capability analysis compared the process variation to the lower and upper specification limits and measured what the customer could experience. A Systems Approach increased the effectiveness of Continued Process Verification (CPV) (Bermejo Higuera, Abad Aramburu, Bermejo Higuera, Sicilia Urban, & Sicilia Montalvo, 2020).

4. CONCLUSION

Conclusions are drawn only on the literature represented for research. It is important to note that a substandard product would not make it to the market, as it would be rejected in testing by the manufacturer. Process capability indices are essential tools for continual improvement of pharmaceutical manufacturing processes where quality of product is of utmost importance. Current trends in process capability analysis including the DMAIC methodology which has benefited several manufacturing processes.

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