Original Article

Process capability improvement using define, measure, analyze, improve, and control approach in the manufacturing of fexofenadine hydrochloride tablet

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ABSTRACT

Aim: Process capability improvement using define, measure, analyze, improve, and control (DMAIC) approach in the manufacturing of fexofenadine hydrochloride (FEX HCL) tablet. **Materials and Methods:** The FEX HCL tablet was formulated by wet granulation method containing the equivalent to 120 mg FEX HCL. Process capability assessment was done by calculating process capability (Cp) and control chart was prepared using quality control parameter of tablets. **Results:** FEX HCL granules were evaluated for angle of repose 25.84 ± 0.50, bulk density 0.42 ± 0.01, tapped density 0.38 ± 0.01, Hausner's ratio 1.04 ± 0.01, and Carr's index 6.25 ± 0.32. Obtained result possessed good flow property. The post-compression evaluation results were found to be: Hardness 3.79 ± 0.12, friability 0.507%, thickness 4.4 ± 0.0.5, drug content 95.99–98.38%, disintegration 129.09 ± 1.65, and *in vitro* release 95.47–99.30% in 30 min. The process capability of the applied procedure was tested by calculating the "Cp" value for drug content, which was found to be 1.15, which means certain modifications are required in the process. Hence, we apply failure, mode, and effect analysis for low drug content process capability and the value of Cp was raised to 6.05. **Conclusion:** After successful implementation of DMAIC approach with the help of process capability analysis, process of FEX HCL tablets manufacturing was improved for Cp = 6.05 compared to previous, i.e., 1.15.

Keywords: Define, measure, analyze, improve, and control, fexofenadine hydrochloride tablets, process capability index, process capability

INTRODUCTION

The pharmaceutical industry is extremely large, dynamic, and one of the most important industries, having an essential role in human's health as well as in welfare of whole society. The manufacturers and the consumers are the main representatives of any industry. The manufacturer tries to produce defect free products meeting the desired specification and the consumer seeks high quality products at the least cost.

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Quality is the primary attribute in the manufacturing that satisfies both the manufacturer and consumer. The pharmaceutical industry is distinguished from other manufacturing industries in aspects of consumers (patients) and heavy research and development investments for drugs. The increase of competitiveness in pharmaceutical industries, made them to use more perfect quality control and quality assurance methods to provide best quality drug products to maintain health of patients. The pharmaceutical industry is mainly suffering from the problems such as poor treatment outcomes, high health bills, treatment failures and deaths, loss of confidence in the health services, enormous economic losses, and national security issue.[1]

Quality improvement is an essential component of modern quality system. Thus, understanding and improving the quality of products

and services has become very important to enhance competitive position and for the growth of business or industry. Hence, the quality improvement program should be applied within an organization and manufacturing area to improve the product quality. To meet all customer and regulatory requirements and to respond to challenges in market, the pharmaceutical companies are looking for solutions to reduce internal cost, reduce defective products, and accelerate the cycle time of products to market, while ensuring regulatory as well as customer compliance.[2]

In process improvement approaches, process capability index is a statistical measure of ability of a manufacturing process to produce the products/outputs within specification. It compares the "Voice of the Customer" (VOC) with the "Voice of the Process". VOC is based on customer requirements and defined as specification limits of process. Voice of process is defined by control limits which are based on process performance.[3]

Define, measure, analyze, improve, and control (DMAIC) is the improvement methodology of six sigma, used to achieve operational excellence by continuous process and product improvement for existing processes. DMAIC focuses on the efficient use of statistical tools so it is very much successful. DMAIC is most widely used problem solving six sigma methodology used in quality and process improvement.[4]

Table 1: Formulation of fexofenadine hydrochloride tablets

S. No.	Ingredients	Quantity in mg
1	Fexofenadine HCL	120
2	PVP in isopropyl alcohol	25
3	Starch	3.75
4	Sodium lauryl sulfate	6.25
5	Aerosil	2.5
6	MCC	85
7	Talc	3.75
8	Magnesium stearate	3.75

Fexofenadine hydrochloride (FEX HCL) is white crystalline drug used to treat allergic symptoms.[5] FEX HCL tablets were manufactured by wet granulation methods to study improvement in process capability.

MATERIALS AND METHODS

Materials

FEX HCL was obtained as gift sample from La Pharma, Ludhiana, Punjab, India. PVP K 30 and sodium lauryl sulfate were purchased from LobaChemie Private Limited, Maharashtra, India. Microcrystalline cellulose, magnesium stearate, and potassium dihydrogen phosphate were purchased from HiMedia Laboratories Private Limited Mumbai, India. All the ingredients were of analytical grade.

Methods

Tablets were formulated as per the formula given in Table 1. All ingredients were passed through 40 mesh size to get uniform size particle and weighed accurately. The drug and all additives such as Sodium Lauryl Sulfate, MCC, Starch, and Aerosil were mixed in a pestle mortar. The 10% solution of PVP in 100 ml isopropyl alcohol was prepared. It was used as a binding solution. The granules were prepared by wet granulation method, using PVP as a binding agent. The granules were dried in hot air oven at 70°C for 10 min. Talc and magnesium stearate were added as lubricants. The tablets were punched using single punch hand operated tablet punching machine.

Prepared granules of FEX HCL were characterized for pre-compression parameters such as angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index. Talc and magnesium stearate were added as lubricants. The tablets were compressed using

Table 2: Evaluation of fexofenadine hydrochloride granules

Batch No.	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index
B1	25.48±1.20	0.45±0.02	0.38±0.03	1.02±0.01	6.64±0.76
B2	26.69±0.94	0.42±0.04	0.36±0.01	1.05±0.02	6.22±0.99
B3	26.44±1.13	0.39±0.02	0.38±0.04	1.03±0.02	5.84±0.85
B4	26.25±1.10	0.40±0.03	0.39±0.03	1.04±0.03	6.06±0.75
B5	26.36±0.40	0.42±0.04	0.37±0.02	1.04±0.02	6.58±0.80
B6	27.29±0.05	0.41±0.03	0.36±0.03	1.04±0.02	6.69±0.45
B7	25.93±0.51	0.44±0.03	0.38±0.03	1.02±0.01	5.37±0.04
B8	25.99±0.65	0.44±0.04	0.38±0.05	1.02±0.02	6.25±0.84
B9	25.23±1.85	0.43±0.04	0.40±0.02	1.02±0.01	6.01±0.74
B10	24.77±0.54	0.41±0.04	0.39±0.04	1.03±0.01	6.90±0.49
B11	26.51±0.49	0.44±0.03	0.41±0.03	1.04±0.02	6.01±1.04
B12	24.56±1.71	0.40±0.02	0.38±0.05	1.02±0.02	6.17±0.94
B13	26.36±1.01	0.41±0.04	0.38±0.03	1.03±0.02	6.44±1.03
B14	26.84±0.48	0.40±0.03	0.37±0.02	1.04±0.01	6.55±1.21
B15	25.96±1.18	0.42±0.05	0.37±0.04	1.04±0.01	5.91±0.59
B16	27.06±0.29	0.44±0.02	0.39±0.02	1.03±0.02	6.62±0.54
B17	25.24±1.64	0.42±0.04	0.39±0.03	1.04±0.03	6.43±0.98
B18	24.50±0.54	0.43±0.04	0.38±0.04	1.03±0.02	6.83±1.06
B19	25.26±0.19	0.42±0.02	0.38±0.02	1.04±0.03	6.24±0.97
B20	25.76±0.80	0.42±0.04	0.37±0.02	1.03±0.01	7.02±0.44

single punch hand operated tablet punching machine. Then, tablets were characterized for hardness, friability, thickness, drug content, disintegration, and *in vitro* release.

The FEX HCL tablet was formulated by wet granulation method containing the equivalent to 120 mg FEX HCL. The process capability assessment was done by calculating process capability (Cp) and control chart were prepared using quality control parameter of tablets.

RESULTS AND DISCUSSION

FEX HCL granules were prepared and were evaluated. The results of evaluated parameters were found to be: Angle of repose 25.84 ± 0.50, bulk density 0.42 ± 0.01, tapped density 0.38 ± 0.01, Hausner's ratio 1.04 ± 0.01, and Carr's index 6.25 ± 0.32. The obtained result possessed good flow property [Table 2].

The post-compression evaluation results were found to be: Hardness 3.79 ± 0.12, friability 0.507%, thickness 4.4 ± 0.0.5, drug content 95.99–98.38%, disintegration 129.09 ± 1.65, and *in vitro* release 95.47–99.30% in 30 min. The process capability of the applied procedure was tested by calculating the "Cp" value for drug content, which was found to be 1.15, which means certain modifications are required in the process [Table 3].

Drug content

Drug content of FEX HCL tablet was done with UV spectrophotometer and drug content was estimated. The drug content of FEX HCL tablet reported 95.99–98.38%, as shown in Table 4 which was found to be within official limits as per IP.

Table 3: Evaluation of fexofenadine hydrochloride tablets

Batch No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (s)
B1	264.33±6.44	4.50±0.09	3.48±0.44	0.45	127.17±4.88
B2	262.00±5.93	4.35±0.05	3.83±0.41	0.53	129.00±5.62
B3	260.17±8.84	4.57±0.05	4.03±0.37	0.49	131.17±6.71
B4	257.33±5.01	4.52±0.08	3.82±0.29	0.57	127.83±7.22
B5	258.33±4.97	4.38±0.08	3.62±0.24	0.68	132.67±6.98
B6	261.50±5.21	4.50±0.09	3.40±0.36	0.62	129.67±5.13
B7	260.67±8.94	4.52±0.08	3.73±0.59	0.53	130.17±4.31
B8	259.33±5.43	4.43±0.08	4.25±0.32	0.65	129.17±4.22
B9	264.00±8.05	4.55±0.05	3.57±0.44	0.38	134.17±7.31
B10	258.50±3.83	4.45±0.05	3.68±0.26	0.44	131.17±6.82
B11	262.83±2.04	4.47±0.12	4.17±0.11	0.61	130.33±5.96
B12	258.83±6.74	4.40±0.06	3.60±0.70	0.53	128.33±4.08
B13	256.17±5.38	4.45±0.05	3.55±0.37	0.39	128.83±7.60
B14	262.33±5.13	4.45±0.05	3.73±0.52	0.35	127.50±9.25
B15	263.50±7.74	4.45±0.05	4.03±0.20	0.42	128.33±6.38
B16	257.17±7.81	4.52±0.10	3.63±0.38	0.52	126.50±3.78
B17	261.00±6.78	4.55±0.05	3.93±0.47	0.47	130.50±4.72
B18	258.50±6.86	4.45±0.05	4.07±0.43	0.61	128.50±5.72
B19	264.00±0.89	4.45±0.05	3.82±0.38	0.52	128.83±7.60
B20	256.17±7.63	4.45±0.05	3.78±0.58	0.67	128.00±4.56

In vitro release of FEX HCL tablets

It was observed that FEX HCL tablet has shown the drug release in 10 min 72.90–78.89% and in 30 min 95.47–99.30%, as shown in Table 5.

Process capability assessment

FEX HCL tablets of drug content values were analyzed by construction of control charts. Control chart of drug content of FEX HCL tablets shows "cp" value 1.15 is shown in Figure 1.

Table 4: Drug content of fexofenadine hydrochloride tablets

Batch No.	Tablet			Mean	SD
	1	2	3		
B1	95.56	95.32	95.74	95.54	0.21
B2	98.75	98.11	98.47	98.44	0.32
B3	95.79	95.45	95.55	95.60	0.17
B4	96.81	96.68	96.12	96.54	0.37
B5	98.93	98.73	98.47	98.71	0.23
B6	99.21	99.37	99.62	99.40	0.21
B7	98.31	98.31	98.68	98.43	0.21
B8	97.73	97.52	97.28	97.51	0.23
B9	98.45	98.51	98.56	98.51	0.06
B10	96.21	97.11	96.62	96.65	0.45
B11	97.47	97.89	97.79	97.72	0.22
B12	98.47	98.76	98.22	98.48	0.27
B13	98.73	98.27	98.56	98.52	0.23
B14	97.35	97.58	97.15	97.36	0.22
B15	96.31	96.53	96.11	96.32	0.21
B16	97.33	97.67	97.21	97.40	0.24
B17	95.37	95.21	96.52	95.70	0.27
B18	97.47	97.15	97.71	97.44	0.28
B19	99.15	99.05	99.42	99.21	0.19
B20	95.32	95.51	95.4	95.41	0.10

Table 5: *In vitro* release of fexofenadine hydrochloride tablets

Batch No.	% Drug release (10 min)	% Drug release (30 min)
B1	77.06±1.69	99.12±0.91
B2	78.13±1.11	98.91±1.08
B3	76.97±1.12	97.32±0.99
B4	77.75±0.67	97.77±0.63
B5	78.19±1.47	98.83±1.04
B6	78.46±0.98	98.54±0.89
B7	78.07±1.34	98.16±0.87
B8	75.36±5.53	99.24±0.78
B9	73.93±5.30	97.47±0.81
B10	77.99±1.48	95.81±1.02
B11	75.45±5.07	99.30±0.72
B12	72.90±4.15	95.75±0.51
B13	73.49±4.44	96.46±1.22
B14	76.87±0.56	97.01±0.58
B15	77.25±1.86	98.85±0.91
B16	77.85±0.87	98.05±1.29
B17	75.32±6.20	98.62±0.59
B18	76.67±1.47	96.14±0.88
B19	77.85±1.16	97.79±0.89
B20	77.47±1.79	97.07±1.17

Table 6: FMEA for low process capability

Process steps	Potential failure mode	Severity (S)	Potential cause	Occurrence (O)	Current control	Detection (D)	RPN (S*O*D)
Dispensing	Wrong dispensing of API and excipients	10	weighing	4	Dispensing quantity being verified	3	120
Mixing	Improper mixing of API and excipients	10	Improper blending time	5	Validate blending time	4	200
Granulation	Granulation time, speed of granulator	9	Improper Granulation time	3	Validate Granulation time	3	81
Compression	Compression speed	8	Improper die filling	3	Validate die filling	4	96

Process capability index

The process capability index for the FEX HCL tablets was found to be 1.15, which is <1.33. So process needs to be improved [Table 2 and Figure 2].

Failure, mode, and effect analysis (FMEA) for low drug content process capability

After finding possible root causes for assay results variation and poor product performance, the most critical factors were prioritized with the help of FMEA. The process FMEA is an approach for prioritizing the possible root causes and identifying the sequence of corrective actions to be taken. The RPN >100 are liable for taking corrective actions. FMEA sheet for FEX HCL tablets manufacturing is tabulated in Table 6.

The value of RPN >100 is for dispensing and mixing variability. Thus, these two are the most critical root cause of drug content variation and should be improved to get high process capability.

Improve phase

The root causes for manufacturing aspects were identified in analyze phase. The potential root causes for problem of lower Cpk of of drug content were identified and prioritized with the help of FMEA. The potential root cause of drug content variation was corrected and improved by making improvement plan to improve the process. The improvement plan was generated and implemented in processes.

Improvement plan

Proper sample weighing in analysis

During analysis, same tablets to be used for drug content test.

Proper check of blending time

Blending time was validated (15–20 min) for proper mixing of the API and excipients.

Control phase

To verify the improvement, ten batches of FEX HCL tablets were manufactured as per the improvement plan and validated. The assay values and other parameters were tabulated and new process capability after improvement was assessed by process capability graphs.

Table 7: Drug content of FEX HCL tablets

Batch No.	% Drug content
B21	97.37±1.39
B22	97.42±1.42
B23	97.08±1.62
B24	97.03±1.44
B25	97.14±0.82
B26	97.53±0.71
B27	97.30±1.43
B28	97.05±1.55
B29	97.25±0.51
B30	97.30±1.25

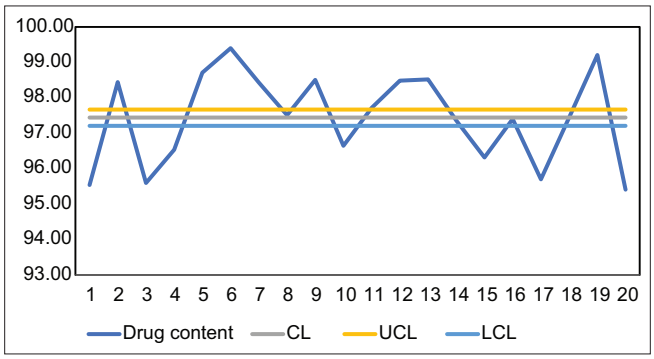

Figure 1: Control chart of drug content of fexofenadine hydrochloride tablets

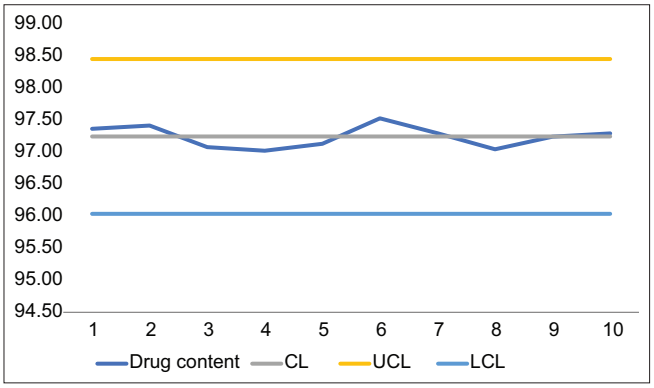

Figure 2: Control chart of drug content of fexofenadine hydrochloride tablets

Process capability improvement

The process capability for the FEX HCL tablets was found to be 1.15, which is <1.33. So process needs to be improved. After improvement in the weighing and mixing, there was improvement in the process, which was measured using Cp value. It was found to be 6.05 for improved process [Figure 2 and Table7].

CONCLUSION

After successful implementation of DMAIC approach with the help of process capability analysis, process of FEX HCL tablets manufacturing was improved for Cp = 6.05 compared to previous, i.e., 1.15.

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