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IMPROVING THE PERFORMANCE OF PHARMACEUTICAL TABLET PRODUCTION USING SIX SIGMA METHODOLOGY (MODULATION ON DIGESTIVE ENZYME TABLET)

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Keywords:

Digestive Enzyme Tablet, Quality control, Six sigma, Performance, Tablet production, Coating solution, Manual cleaning, bacterial count

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ABSTRACT: Each company is expected to develop specifications for their products to be accommodated with the inspection guide of pharmaceutical quality control. After product analysis for (X) pharmaceutical company it was noticed that 84.5% of defects were attributed to tablet department while 14.1% and 1.4% for ampoule and syrup departments respectively so it was valuable to solve the tablet department problems. Data was collected for three months for two types of tablets which were analgesic tablet (AT) and digestive enzyme tablet (D.E.T). D.E.T was chosen for further study due to its high percent of defect. By using six sigma methodology to analyze the collected data it was found that the major problem was in tablet microbiological test 85.9% rather than the physical problem 14.1%. D.E.T was subjected to study the variables affecting the bacterial count like raw material, process environment and microbiological analysis accuracy. It was found 66.7 of the problem caused by the variation in process environment. By using factorial design for three variables it revealed that the cleaning and disinfection methods were the most affecting factor that caused the total variation in the overall process. Seven remedies for cleaning were studied and each remedy was rated for each criterion using a special scaling system. It was noticed that the manual cleaning was the most effective method since it lowered the bacterial count of the coating solution to 285 cfu/ml and affected on sigma level to be 4.2 σ which exceeded the target (not more than 500 cfu /ml). Six Sigma methodology is a promising method for improving the pharmaceutical tablet production and achievement its quality control.

INTRODUCTION: Quality within all industries is important, but within the pharmaceutical industry, it is essential. Because lives are at stake, quality, when it comes to creating and manufacturing medicines for individuals, is necessary[1] since drugs worldwide used either through prescription or as over the counter medication[2]. Since 2002, FDA began an initiative to address cGMP for the 21st century[3].

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cGMP focuses on manufacturing as a mean to produce a safe and effective products for the patient [4]. The practice of industrial hygiene focuses upon the implementation of workplace safety solutions and control of workplace health risks and stressors by highly trained and experienced professionals skilled in the science and art of hazard anticipation, recognitions, evaluation and control within the workplace, the surrounding environment, and community[5].

For drug products, specifications usually consist of test methods and acceptance criteria for assay, impurities, pH, dissolution, moisture, and microbial limits, depending on the dosage forms.

They are usually proposed by the manufacturers and subject to the regulatory approval for use[6]. This effort involved taking new looks at both the regulatory and industrial systems for insuring drug quality[7]. Six Sigma as a measurement standard in product variation can be traced back to the1920's when Walter Shewhart showed that three sigma from the mean is the point where a process requires correction[8]. Six Sigma Projects are based on the DMAIC model. The DMAIC model is the generic model of six sigma methodology. It is an acronym that stands for; Define, Measure, Analyze, Improve and Control. Sometimes this model includes recognize as an awareness item to the model. Each of the components addresses a different aspect of the overall improvement and breakthrough strategy[9].

Six sigma is a statistical concept which helps us to define the problems systematically, provides tools to measure and analyze the influential factors, identifies the improvements that can be implemented easily and ensure that the changes which have been made, are kept alive through a control process and maintains the gains over the time. It is a known fact that in a process with six sigma capability, process variation is not reduces more than 3.4 defects per million opportunities[10]. Six Sigma has evolved over time. It's more than just a quality system like TQM or ISO. It's a way of doing business. As Geoff Tennant describes in his book Six Sigma: SPC and TQM in Manufacturing and Services: "Six Sigma is many things, and it would perhaps be easier to list all the things that Six Sigma quality is not. Six Sigma can be seen as: a vision; a philosophy; a symbol; a metric; a goal; a methodology." We couldn't agree more[11].

The goals of Six Sigma for improving customer satisfaction relay on accelerating process cycle times and time-to-market, reducing defects, controlling variation and improving predictability, reducing costs – without "unintended consequences", and improving end-to-end process management and measurement[12].

The pharmaceutical market in Egypt It started around 1940 when the Misr Company of Pharmaceutical Industries was founded. In the 1980's and 1990's, the Egyptian market was over flooded by a huge amount of private sector pharmaceutical companies.

According to the report of IMS Health (2006), the pharmaceutical organizations in Egypt fall into three categories:

- Public sector categories, the Drug Holding Company (D.H.C.), which have their roots in the first national pharmaceutical Industry
- Local private sector companies.
- Transnational private corporations.

According IMS the pharmaceutical market, in 2006, consists of around 47 pharmaceutical companies, of which 8 are publicly owned. The Egyptian ministry of Investment speak about 30 private and 8 public pharmaceutical companies, source; IMS Health, unpublished Statistical report, March 2007GlaxoSmithKline has the largest market share, an estimated 7.5%, followed by Novartis,6.7% and Sanofi-Aventis which possesses nowadays an estimated 6.3% of the Egyptian pharmaceutical market, due to the international merger of Sanofi and Aventis in August 2004. Sanofi-Aventis is now both the world largest and Egypt's third largest pharmaceutical company and it also ranks number 1 in Europe.

Egypt's exports of pharmaceuticals have grown steadily in recent years, topping USD 270 million in FY2011/2012Compared to USD 238 million in FY 2006/2007. Investments in Egypt's pharmaceutical industry currently stand at EGP 26 billion, with the industry employing a total of 39,500 professional staff and production workers. Egypt has the largest drug manufacturing base in the MENA region accounting for around 30% of the regional market.

Local production covers around 93% of the market with 7% made up of highly specialized pharmaceuticals not produced locally. Annual production is recorded to be EGP15 billion in 2009 in 2010, the market size has reached USD 4.1 billion at retail prices that represented 1.9% of GDP and 30.6% of health expenditure. The number of pharmaceutical factories has increased from 90 factories in 2006 to 120 factories in 2010 with other 70 plants that are under construction[13].

Large multinationals as Glaxo Smith Kline (GSK) is the leading company in the Egyptian market with 9% of the market share. Sanofi-Aventis and Novartis, Pfizer, Servier, and Bristol- Myers are also among the top multinational manufacturers in the market. Holdipharma have 1700 types of medicine, 42.1% of them are sold in cheap prices, with LE 1.3bn. annual losses because of its low prices the total capital of Holdipharma and its affiliates is about LE 2bn, with a cumulative growth rate over the last five years 50%. Egyptian pharmaceutical exports in 2008 reaching US $ 120.4 million. Imports have reaching US $ 1018.4 million in 2008[14].

MATERIALS AND METHODS:

Materials: produced by (X) company:

- Ampoules: sample = 60,000 ampoule/batch.
- Tablets: sample = 3000 tablet/batch.
- Syrup: sample = 1500 bottles/batch.

Methods:

1. **Classification of the company pharmaceutical product formulations Pharmaceutical products were classified into:**

   Sterile products:

   It is the pharmaceutical dosage form that contains therapeutic agent and must be free of microorganism. It includes ampoule production only.

   Non Sterile Products:

   It is the pharmaceutical dosage form that contain therapeutic agent that have microbial loading. It includes tablet and syrup production.

2. **Problem analysis:**

   Samples are pulled from different sections of production (Ampoule – Syrup - Tablets). Samples were drawn from batches to analyze. Result of analysis indicated batch rejection or acceptance according to the specification limit.

3. Data collection and analysis before applying six sigma on tablet department (For Three Months). Two types of tablets were subjected to study their collected data. The first type was analgesic (A.T) tablet and the other was digestive enzyme tablet (D.E.T). Data for both of them were collected and analyzed.

4. Applying six sigma methodology on D.E.T collected data.

Six Sigma projects enhance technological innovation of the firms; however, they are beneficial for firms in stable environments[15]. So this study aims to increase the internal customer satisfaction by identify the main causes of out of specification. The suggested reason was the variation in the Bacterial count of Digestive enzyme tablet (D.E.T) which also caused dramatic effects on the tablet production process due to bacterial count got out of specification. That was reported through internal customer (quality control microbiology). Focus on the processes using six sigma methodology was done to achieve the customers' expectations. The application of six sigma includes the following[16]:

Define Phase:

This phase deals with defining processes, key customer requirements, and process "owners"[11]. At this phase three issues were studied which were:

- Identify Customer Critical to quality.
- Develop Project Charter.
- SIPOC Analysis.

Measure Phase:

This phase considered as measuring performance against customer requirements and key performance indicators[11]. It consists of three main steps:

- Critical to Quality Characteristics.
- Define Performance Standard.
- Measure System Analysis.

Analyze Phase:

This phase was related to Analyze data to enhance measures and refine process management mechanisms[11]. This phase consists of three main steps:

- Establish Process Capability.
- Process Performance.
- Identify Variation Source.

Improve Phase:
The main steps of the improve phase were:

- Generation of Ideas.
- Rating of ideas.
- Design of experiment.
- Improvements recommendation.

Control Phase:
Controlling process performance was done by monitoring process inputs, process operation, and process outputs, and responding quickly to problems and process variations[11]. This phase contained the following:

- Define and Validate Measurements.
- Determine Process Capability.
- Implement Process Control.

5. Implementing Integrated Approach of Six-Sigma at tablet coating solution**.**

6. Manual cleaning.

RESULT AND DISCUSSION:
Company products were classified into sterile and non sterile. The sterile product was ampoule and the non sterile subdivided into tablet and syrup. **Table 1** showed the problem analysis of the products for one month production.

TABLE 1: PROBLEM BATCH ANALYSIS

Departments	Number of items/batch	Samples/ batch	Number of batches	Number of items non conform	Number of batches non conform	Problem sorting
Ampoule	600,000 Ampoules	60,000 Ampoules	15 Batches	1,000 Ampoules	-----	Physical
Tablets	30,000 Tablets	3,000 Tablets	30 Batches	6,000 Tablets	5 Batches	Microbiology
Syrup	15,000 Bottles	1,500 Bottles	15 Batches	100 Bottles	1 Batches	Microbiology

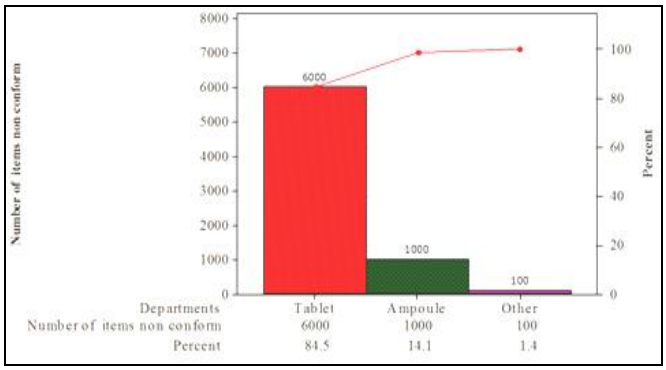

FIG.1: PARETO CHART DEPARTMENTS DEFECTS ANALYSIS

As shown from **Fig.1** 84.5% of the defects were attributed to tablet department that's considered the biggest problem rather than the other departments. Ampoule and syrup departments defect ratios were 14.1 and 1.4% respectively. The previous data showed that the major problem was related to tablet department. The sorting of tablet department data revealed that 14.1% of the tablet defect was related to physical problem and 85.9% was related to microbiological problem so the main issue for further study was the defect related to microbiological reason. Data was collected for three months for both of D.E.T and A.T for further analysis. As shown in **Table 2** the microbiology defect and nonconformity for the digestive enzyme tablet was higher than the analgesic tablet.

Digestive enzyme tablet was taken for further study. Process analysis for digestive enzyme tablet was done to recognize the reasons of the microbiological defect. **Table 3** and **Fig.2** showed that the main reason for the highly bacterial count was the coating solution since it had 80% of the total bacterial count. So we had to solve the problem of the coating process to improve the tablet process.

TABLE 2: DATA COLLECTION OF TABLET DEPARTMENT FOR THREE MONTHS

Date	Batch Number	Type of Tablet	Quantity	Sample	CFU/g	Conclusion
31/12/2012	A001	(A.T)	2000 tablets	200 tablets	1300	Non conform
	D001	(D.E.T)	1000 tablets	100 tablets	810	Conform
03/01/2013	A002	(A.T)	2010 tablets	200 tablets	850	Conform
	D002	(D.E.T)	990 tablets	100 tablets	1240	Non conform
06/01/2013	A003	(A.T)	1980 tablets	200 tablets	400	Conform
	D003	(D.E.T)	1010 tablets	100 tablets	1100	Non conform

09/01/2013	A004	(A.T)	2020 tablets	200 tablets	960	Conform
	D004	(D.E.T)	980 tablets	100 tablets	980	Conform
12/01/2013	A005	(A.T)	1990 tablets	200 tablets	750	Conform
	D005	(D.E.T)	970 tablets	100 tablets	1200	Non conform
15/01/2013	A006	(A.T)	1000 tablets	200 tablets	1350	Non conform
	D006	(D.E.T)	2020 tablets	100 tablets	1410	Non conform
18/01/2013	A007	(A.T)	1995 tablets	200 tablets	850	Conform
	D007	(D.E.T)	1020 tablets	100 tablets	1400	Non conform
21/01/2013	A008	(A.T)	2040 tablets	200 tablets	1240	Non conform
	D008	(D.E.T)	995 tablets	100 tablets	950	Conform
24/01/2013	A010	(A.T)	2000 tablets	200 tablets	900	Conform
	D010	(D.E.T)	990 tablets	100 tablets	1360	Non conform
27/01/2013	A011	(A.T)	2010 tablets	200 tablets	800	Conform
	D011	(D.E.T)	986 tablets	100 tablets	1400	Non conform
30/01/2013	A012	(A.T)	2000 tablets	200 tablets	850	Conform
	D012	(D.E.T)	1000 tablets	100 tablets	1320	Non conform
02/02/2013	A013	(A.T)	1996 tablets	200 tablets	900	Conform
	D013	(D.E.T)	987 tablets	100 tablets	980	Conform
05/02/2013	A014	(A.T)	2030 tablets	200 tablets	1100	Non conform
	D014	(D.E.T)	1000 tablets	100 tablets	1300	Non conform
08/02/2013	A015	(A.T)	2020 tablets	200 tablets	940	Conform
	D015	(D.E.T)	989 tablets	100 tablets	1210	Non conform
11/02/2013	A016	(A.T)	2020 tablets	200 tablets	1110	Non conform
	D016	(D.E.T)	998 tablets	100 tablets	1250	Non conform
14/02/2013	A017	(A.T)	1984 tablets	200 tablets	910	Conform
	D017	(D.E.T)	1000 tablets	100 tablets	1380	Non conform
17/02/2013	A018	(A.T)	1991 tablets	200 tablets	830	Conform
	D018	(D.E.T)	996 tablets	100 tablets	1200	Non conform
21/02/2013	A019	(A.T)	1998 tablets	200 tablets	760	Conform
	D019	(D.E.T)	1000 tablets	100 tablets	1300	Non conform
24/02/2013	A020	(A.T)	2000 tablets	200 tablets	880	Conform
	D020	(D.E.T)	992 tablets	100 tablets	970	Non conform
27/02/2013	A021	(A.T)	2000 tablets	200 tablets	920	Conform
	D021	(D.E.T)	1000 tablets	100 tablets	1360	Non conform
02/03/2013	A022	(A.T)	1993 tablets	200 tablets	880	Conform
	D022	(D.E.T)	1000 tablets	100 tablets	1330	Non conform
05/03/2013	A023	(A.T)	2020 tablets	200 tablets	650	Conform
	D023	(D.E.T)	996 tablets	100 tablets	1330	Non conform
08/03/2013	A024	(A.T)	1998 tablets	200 tablets	660	Conform
	D024	(D.E.T)	997 tablets	100 tablets	1200	Non conform
11/03/2013	A025	(A.T)	1996 tablets	200 tablets	850	Conform
	D025	(D.E.T)	998 tablets	100 tablets	1250	Non conform
14/03/2013	A026	(A.T)	2040 tablets	200 tablets	900	Conform
	D026	(D.E.T)	1030 tablets	100 tablets	1360	Non conform
17/03/2013	A027	(A.T)	2010 tablets	200 tablets	670	Conform
	D027	(D.E.T)	1050 tablets	100 tablets	1400	Non conform
21/03/2013	A028	(A.T)	2005 tablets	200 tablets	890	Conform
	D028	(D.E.T)	1040 tablets	100 tablets	940	Conform
24/03/2013	A029	(A.T)	2005 tablets	200 tablets	830	Conform
	D029	(D.E.T)	1000 tablets	100 tablets	1550	Non conform
27/03/2013	A030	(A.T)	2000 tablets	200 tablets	840	Conform
	D030	(D.E.T)	1000 tablets	100 tablets	980	Conform

TABLE 3: PROCESS ANALYSIS OF D.E.T

	Process steps	Samples examination	Bacterial count / gram
Raw Materials	Microcrystalline cellulose	10 grams taken from every raw material	10 CFU/g
	Talc powder		30 CFU/g
	Lactose monohydrate		40 CFU/g
	Magnesium stearate		70 CFU/g
	Pepsin		60 CFU/g
	Panceatin		20 CFU/g
Water analysis		One ml from sample	10 CFU/ml
Powder after blinding		10 grams from different location	50 CFU/g
Tablet after compression			100 CFU/g
Tablet after coating			1600 CFU/g

Six Sigma fundamental phases (define, measure, analyze, improve and control) applied on the problem of D.E.T in tablet production line through defining the scope and goals of improvement, measuring the process and analyze the problem.

This study aimed to increase the internal customer satisfaction by identifying the main reasons led to out of specification focusing on the processes using six sigma methodology.

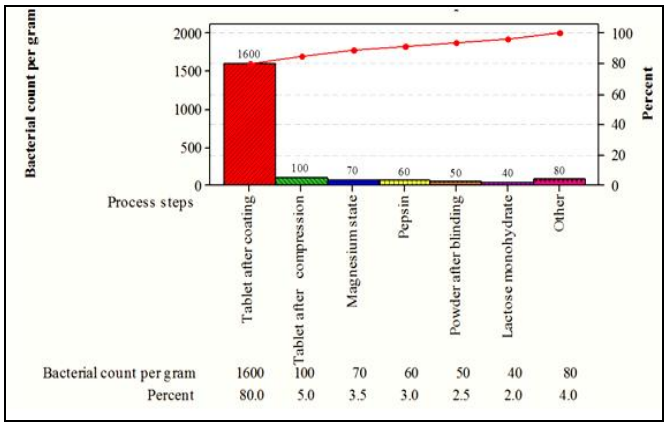

FIG.2: PARETO CHART FOR PROCESS ANALYSIS OF TABLET

TABLE 4: PROJECT TIME PLAN

Phase	2013											
	1	2	3	4	5	6	7	8	9	10	11	12
Define												
Measure												
Analysis												
Improve												
Control												

Table 4 showed the project time frame for the five phases. The define phase concerned with identify the customer. Customer was classified into:

i)Internal Customer, quality control microbiologist who was responsible for microbiological analysis at sterile product drug as ampoule and non-sterile drug as syrup and tablet (D.E.T), (A.T).

ii) External Customer, Ministry of Health, public hospitals, private hospitals, and medical centers.

Customer critical to quality (CTQ) was the internal customer for three variables which were:

i) Raw material, which revealed that the microbiological analysis of raw materials was required to meet specification of analysis, raw materials that were internal process.

ii) Process environment, which was proceeded during the manufacturing production areas have ability to causes contamination of (D.E.T).

iii) Microbiological analysis accuracy, which reported that all microbiological tests must be under sterile aseptic conditions (sterilized equipment, laminar air flow, microbiologist free from infection pathogen). Technical process flow chart was prepared by dividing the production process into four phases as the following: raw material, compression, coating, and blistering and packaging. After a deeply look through the detailed process steps a process drill down tree was developed as shown in **Fig.3.**

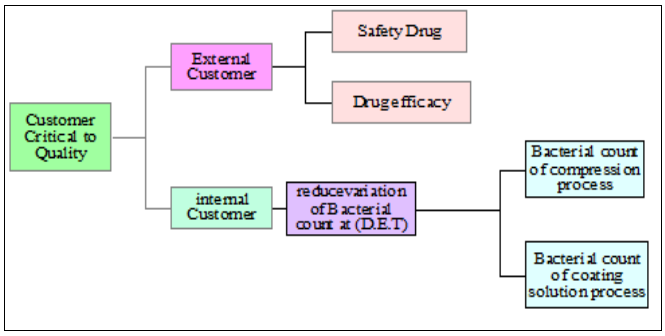

FIG.3: TABLET (D.E.T) PRODUCTION PROCESS DRILL DOWN TREE

The project leader selected the team indicated the business case, mentioned the problem statement, indicated the goal statement, indicated the project scope, and put the project time plan for each phase to implement six sigma projects as shown in **Table 5.**

TABLE 5: PROJECT CHARACTER

Project Character	
Project Leader :	**Team Member:**
The researcher.	Quality control microbiology team leader.
Business Case:	Production members.
To eliminate the defect in the (D.E.T) process.	Quality assurance member.
Problem Statement: Reduce the bacterial count of digestive enzyme tablet (D.E.T) that lead to causes customer satisfaction of internal customer to give safe drug to patient.	Goal Statement: Reduce the bacterial count of (D.E.T) to be not more than 1000 cfu/g by the determine the root causes of the variability of (D.E.T) which will lead to achieve after eight months.

The team was selected to represent the main branches affecting the (D.E.T) production on the selected tablet. The following individuals were responsible for the production process of (D.E.T) with high quality and were chosen according to their awareness and responsibility of work in each of the four processes of the (D.E.T) production process.

- **Quality Controls Team Leader:** Responsible for follow up of all quality activities in the selected (D.E.T) production and the

microbiological lab for the company.

- **Production Shift Leader:** Responsible for distributing workload among the workshop and tablet production in the company.

- **Planning & Scheduling Team Leader:** Ensure that the projects achieve their goals on schedule.

- **Supply Manager:** Responsible for ordering and follows up of all departments.

A SIPOC Process Definition helps the Process Owner and those working on the process to agree the boundaries of what they will be working on. It provides a structured way to discuss the process and get consensus on what it involves before rushing off and drawing process maps[17].

So the SIPOC diagram was prepared to provide a summary of the key factors of the process (D.E.T). The SIPOC simply was identified to ensure that selected employees in this project were aware with the problem parts as shown in **Fig 4**.

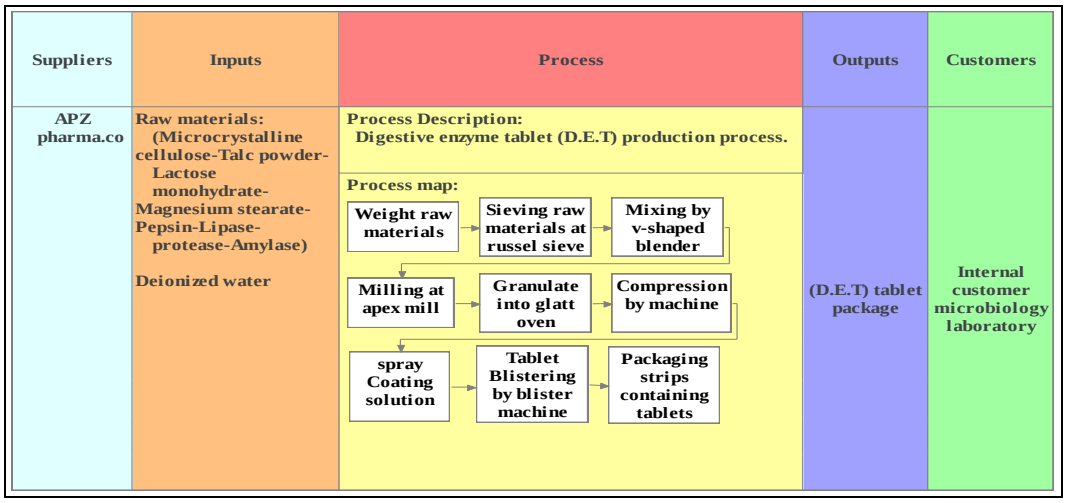

FIG.4: SIPOC ANALYSIS

The team focused on how to reach the main defects in the (D.E.T) production process to determine root causes of (D.E.T). The measure phase consisted of three main steps which are critical to quality, define performance standard, and measure system analysis. The main factors effecting the tablet composition and bacterial count variation from microbiological point of view was coating solution which measured by CFU/g. The team studied the data collected from September 2012 to October 2012.

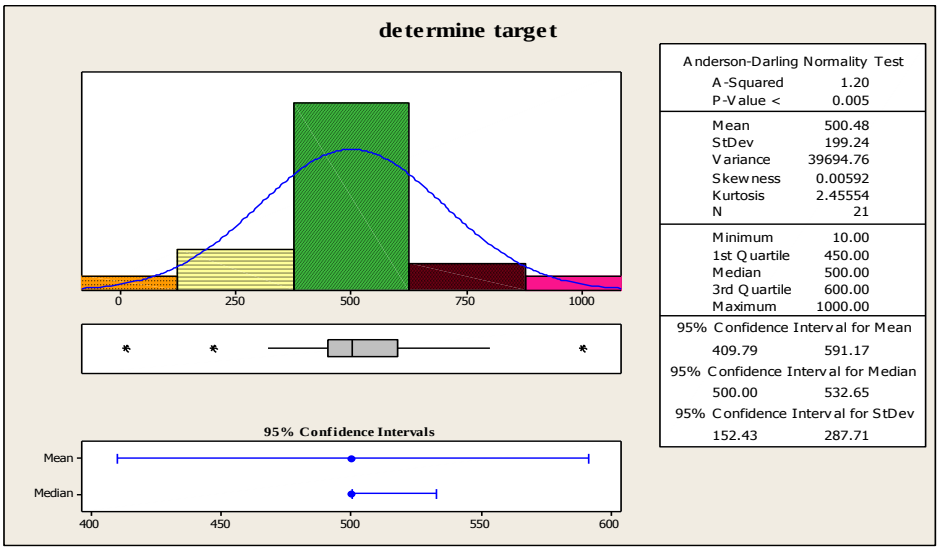

FIG.5: TARGET DETERMINATION

As shown in **Fig.5** the median was centered in the IQR box. The confidence intervals for the precipitated data indicated that 95% confident that: The mean was 500.48; standard deviation was 199.24 which revealed that on average, the values of data tended to differ from the mean by ±199.24. Q1 was 450, Q3 was 600 and the IQR was 150. The maximum value was 1000, minimum value was 10 and the range was 990 so the lower specification limit LSL would be 10 cfu/g, and upper specification limit would be 1000 cfu/g, target would be 500 cfu/ml, and as the standard deviation of coating solution of the (D.E.T) feed according to the company quality control requirement was 500 cfu/ml to keep the bacterial count of (D.E.T) at safety limits. The defect was defined as the value of the bacteria of (D.E.T) process that had to be more than 1000 cfu/g for the selected tablet productions. Run Chart and individual control chart were done as shown in **Fig. 6, 7.**

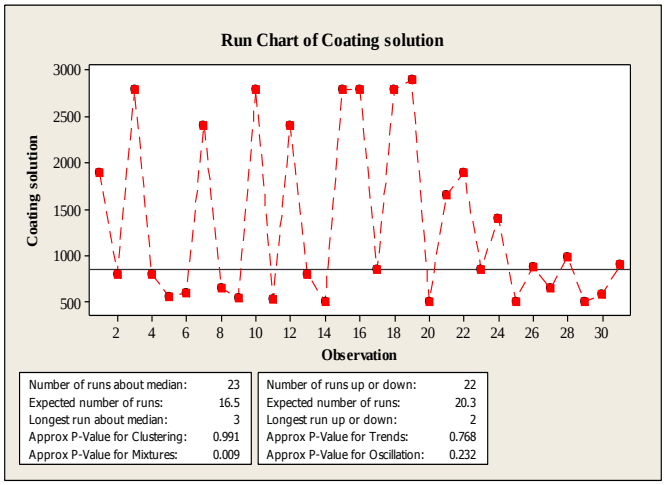

FIG. 6: RUN CHART OF COATING SOLUTION

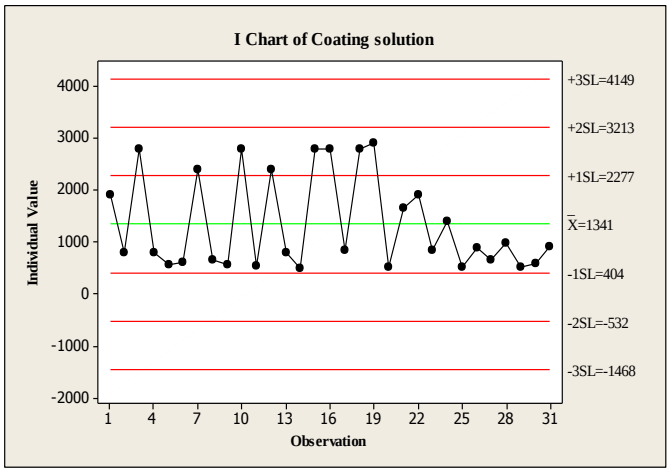

FIG.7: I CHART OF COATING SOLUTION

As shown in **Fig. 6, 7** the average of the Standard deviation of bacterial count of (D.E.T) during the measure period was 1341which was out of the company quality control reference limits (standard deviation of bacterial count was 500cfu/ml) which gave an indication for high variation on (D.E.T). Regarding to the analysis phase in term of establish process capability since there was process instability so there was no need to study the capability of the process, ppm is equal to 387096, so sigma levels 1.77 that's give yield 60.85%.

The process performance showed a gap between the current state for the standard deviation of coating solution (512) and the target from the study (500) which is less than the specification of the company (not more than 1000)**.** Identification of the variation sources was obtained by Study the measured values of standard deviation of coating solution during the period April to June 2013, and he found that 12 measured values from 31 are out of limit, Meeting with the team member and brainstorming take place with the selected company team to review the problems and factors that may be affect the variability of the kiln feed during taking the samples.

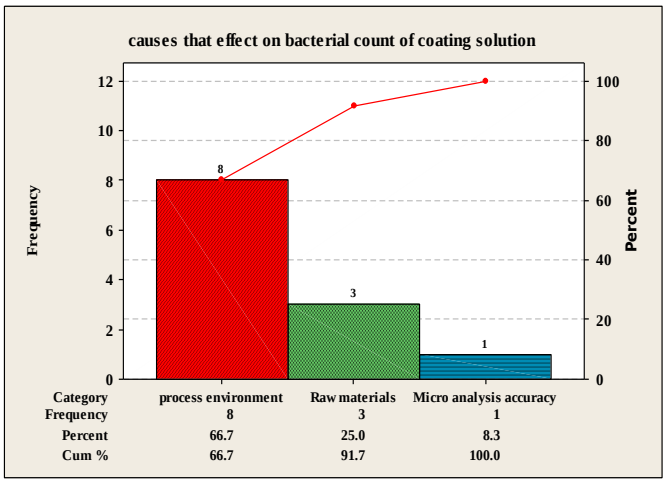

FIG.8: CAUSES THAT AFFECT THE BACTERIAL COUNT OF COATING SOLUTION

As shown at **Fig. 8** the data was collected from the team revealed that the source of variation was the process environment. By using cause effect study on the mentioned variable as in **Fig. 9** it was noticed that Raw materials for pharmaceutical products was a source for some forms of microbial growth, depending on the nutritive properties and moisture contents**.** Peoples who involved on every

step of all process in manufacturing areas of (D.E.T) affected on bacterial count. Methods of analysis used to ensure that contamination of the manufacturing process is kept under control, with frequency of environmental analysis. Sterile petri dishes containing (T.S.A) media were added on production areas (compression, coating solution preparation, and packaging area) to evaluate air contamination. Swabs were taken from the machinery parts and walls before and after cleaning and sterilization to assess cleaning and disinfection method and evaluation of personnel Gown. Finger print was used to evaluate personnel hygiene through applying personnel fingers on sterile petri dish containing (T.S.A) media. Machine and equipment were very important factors in contamination control because it's direct contact with drug in every step of processes, so through cleaning and disinfection and control of air supply with gown and hygiene control could lead to decrease bacterial count. Environment was include deionized water system that are used in process and cleaning, and air supplementation which was direct proportional on bacterial count in machine and equipment and keep personnel hygiene with disinfection.

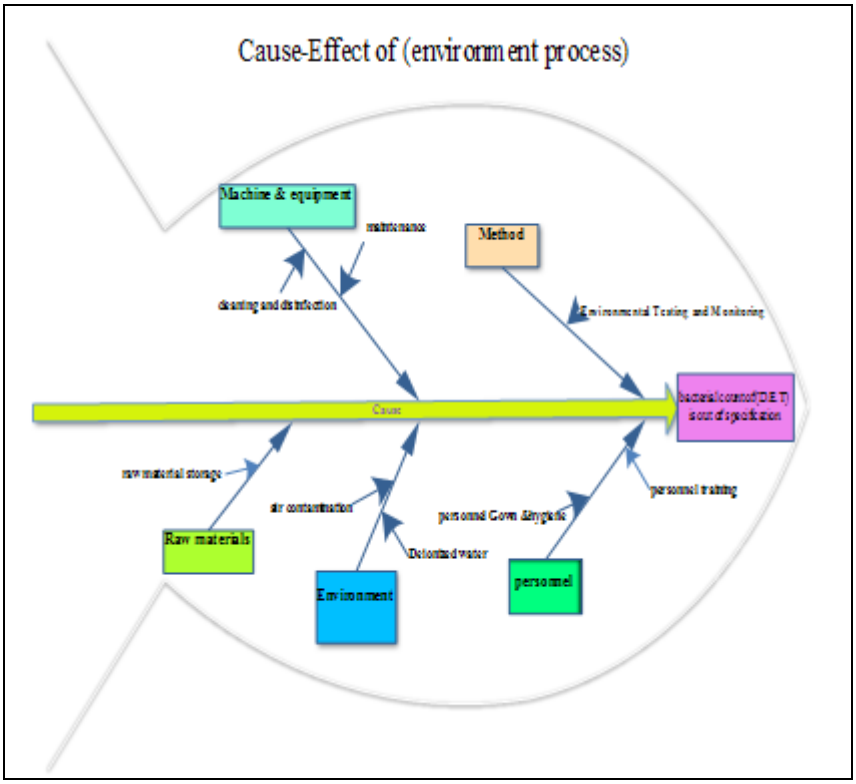

FIG.9: CAUSE-EFFECT DIAGRAM OF ENVIRONMENT PROCESS

Improvement phase of (D.E.T) production line were done by generation of ideas as shown in **Fig. 9**. One of the three vital factors which was necessary and vital to be eliminated (air contamination), the other two factors are personnel gown & hygiene, and parameters that need to be increased or decreased (increase technicians experience and reduce the time spent in documentations recording).

A design of experiments with two levels, full factorial design was performed to test the significance of the suggested vital factors and the interaction between them. Three factors (Changing the training method, increase technicians experience and reduce the time spent in documentations recording) are put into experiment with two possible levels for each factor, as in **Table 6.**

TABLE 6: FACTORS LEVELS

Factor	Level 1 (-1)	Level 2 (1)
Air supply	Ordinary air supply	Applying HVAC system
Personnel gown & hygiene	Use disinfectant with cleaning gown	Sterilization gown with disinfectant
Cleaning & disinfection method	Effective method	Applying another method

The level of each factor had to be-identified in order to know the actual meaning of each factor and level before applying the experiment. Air supply divided into two levels, the first level is the air contamination, which means that, uncontrollable bacterial count in tablet manufacturing. The second level is Applying HVAC system, which means that, air will prevent aerosol contamination by bacterial spores, and mold these can be achieve through applying HVAC system in tablet manufacturing. Obviously, the second level is the proper level in the first factor. Personnel Gown & Hygiene divided into two levels; the first level is uncontrolled personnel gown & hygiene, which means that, the personnel gown & hygiene holds a number of microbes that may interference of tablet through direct contact.

The second level is a personnel control gown & hygiene, which mean that reduces the microbial load on Gown and prevents bad behavior of personnel's. Obviously, the second level is the proper level in the second factor. Cleaning and disinfection method divided into two levels, the first level is the unregulated cleaning and disinfection , which means that cleaning is prevent product integrity, remove dust , any waste can be carried microorganisms, disinfect are used to kill microorganisms in environment and on personnel's obviously, the second level is the proper level in the third factor.

Experiments had performed in the (D.E.T) production of coating solution and microbiological samples collected from these areas and transferred to microbiology laboratory to be examined by plate count method, all testes were happened under sterile equipment's and under laminar air flow. Experiment results were as shown in **Table 7** below.

TABLE 7: FACTORIAL DESIGN EXPERIMENT RESULTS

Run order	Air supply	Personnel gown & hygiene	Cleaning & disinfection	Bacterial count / plate
1	Ordinary air supply	Use disinfectant with cleaning gown	Applying another method	700
2	Applying HVC system	Use disinfectant with cleaning gown	Effective method	350
3	Ordinary air supply	sterilization disinfectant with cleaning gown	Applying another method	650
4	Applying HVC system	Use disinfectant with cleaning gown	Applying another method	370
5	Applying HVC system	sterilization gown with disinfectant	Applying another method	360
6	Ordinary air supply	sterilization gown with disinfectant	Applying another method	750
7	Applying HVC system	sterilization gown with disinfectant	Applying another method	300
8	Ordinary air supply	Use disinfectant with cleaning gown	Applying another method	800

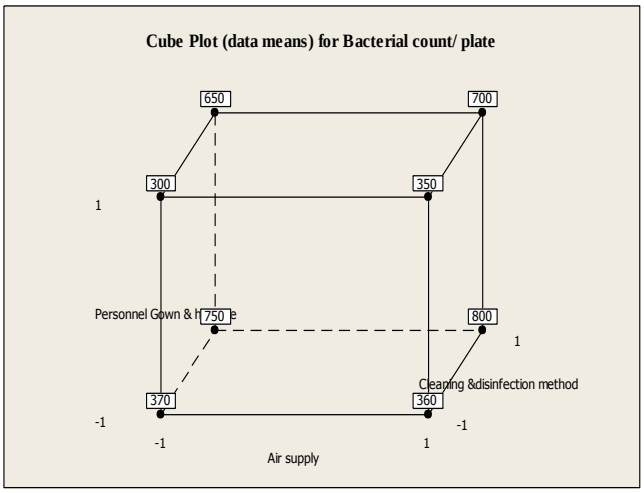

FIG. 10: EXPERIMENT RESULT CUBE REPRESENTATION

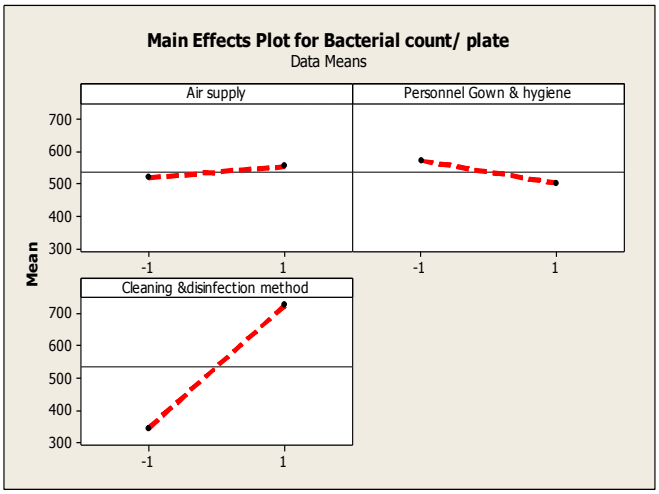

FIG.11: EXPERIMENT'S FACTORS VARIATION

As illustrated in **Fig. 10, 11** the cleaning & disinfection method was the most affecting factor that caused the total variation in the overall process.

Improvement Methodology (Cleaning and disinfection method):

Disinfection is a process that reduces the number of pathogenic microorganism with an inanimate object to a level, which is not harmful to health, It is generally more reliable than chemical processes, leaves no residues, is nontoxic, shows lack of emergence of resistance, and the process is automated and validated, similar to the process of sterilization. Several remedies for cleaning process were studied as shown in **Table 8**.

TABLE 8: REMEDIES OF CLEANING PROCESS

Cleaning methods	Advantage	Disadvantage
Clean in place	•Designed for clean ability. •Automated. •Consistency. •Water/cleaner savings. •Time saving. •Equipment wear. •Ease of validation. •Automation. •The lack of assembly/disassembly. •Safety of operators.	•Luck of flexibility. •High initial capital cost. •Use of more aggressive cleaning agents.
Agitated immersion	•Low capital cost. •Simplicity.	•Process time. •Water and cleaning agent use. •Equipment limitations.
Automated parts washing	•Consistent performance. •Chemical and water savings. •Safety.	•Initial capital cost. •Unsuitable for delicate parts.
Ultrasonic washer	•Excellent cleaning for delicate items. •Low initial capital cost.	•Significant manual processing. •Validation issues.
High pressure spraying	•Relatively low capital cost. •Highly effective.	•Large water use. •Equipment limitations. •Variability of manual systems.
Static immersion	•Low capital cost. •Simplicity.	•Process time. •Water and cleaning agent use. •Equipment limitation.
Manual cleaning	•Simplicity. •Flexibility. •Low cleaning agent cost.	•Inherent variability.

As shown in previous table the seventh remedy (manual cleaning) was the best solution as it has a solution for all problems, but with some of competition with remedy one especially that the (cleaning in place) in terms of will reduce process contamination, easy to implement, so the team also approved the first remedy. Selection between the two remedies was done by using selection matrix

Table 9. In remedy selection matrix, each remedy had been rated for each criteria using 1-2-3 scale.

- Bad remedy at this criterion.
- Not bad and not good remedy at this criterion.
- Good remedy at this criterion.

TABLE 9: REMEDY SELECTION MATRIX

Criterion	Remedy 1 Clean in place	Remedy 2 Agitated immersion	Remedy 3 Automated parts washing	Remedy 4 Ultrasonic washers	Remedy 5 High pressure spraying	Remedy 6 Static	Remedy 7 Manual cleaning
Cost	1	1	2	1	1	1	3
Microbial contamination control	3	1	3	2	1	2	3
Temperature control	3	1	2	1	1	1	3
Safety for operator	3	1	2	2	1	1	3
Automated	3	1	3	1	2	1	2
Total	**13**	**5**	**12**	**7**	**6**	**6**	**14**

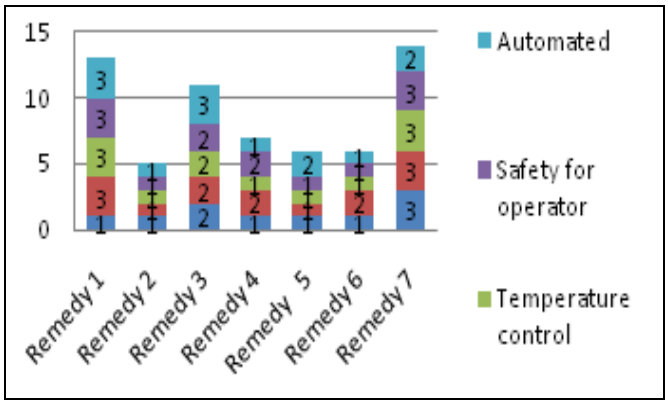

FIG.12: REMEDY SELECTION MATRIX

As shown from **Fig. 12** the most suitable cleaning method was manual cleaning.

Control Phase.

This phase explains the implementation of Six-Sigma control phase. A measurement bacterial count had been developed, implemented and carried out on a three months to measure standard deviation of bacterial count at (D.E.T) at all process. The bacterial count relied on the formation of the (D.E.T).

TABLE 10: CONTROL PHASE MEASUREMENT RESULTS

Date	Microcrystal line	Take powder	Lactose monohydrate	Pepsin	Pancreatine	Coating solution	σ
1 Sep. 13	320	300	40	60	345	300	227.5
3 Sep. 13	410	380	45	65	160	300	226.6666667
6 Sep. 13	305	230	50	75	70	350	180
9 Sep. 13	115	20	60	80	100	200	95.8333333
12 Sep. 13	125	10	70	85	120	100	85
15 Sep. 13	335	15	30	40	120	200	123.3333333
18 Sep. 13	45	30	40	345	200	100	126.6666667
21 Sep. 13	30	320	60	360	345	300	235.8333333
24 Sep. 13	325	330	30	330	60	350	237.5
27 Sep. 13	55	40	220	100	70	260	124.1666667
30 Sep. 13	65	50	40	40	80	380	109.1666667
3 Oct. 13	75	30	45	30	90	280	91.6666667
6 Oct. 13	10	10	60	35	60	180	59.1666667
9 Oct. 13	25	15	170	340	70	300	153.3333333
12 Oct. 13	45	330	315	45	75	360	70
15 Oct. 13	185	120	15	360	85	410	195.8333333
18 Oct. 13	50	25	25	30	90	200	70
21 Oct. 13	35	30	35	20	200	260	96.6666667
24 Oct. 13	40	45	40	10	30	300	77.5
27 Oct. 13	30	80	45	405	40	200	133.3333333
30 Oct. 13	40	100	65	40	100	100	74.1666667
2 Nov. 13	45	25	100	60	120	210	93.3333333
5 Nov. 13	60	85	80	65	150	300	123.3333333
8 Nov. 13	470	30	445	70	170	320	250.8333333
11 Nov. 13	85	35	335	280	180	290	200.8333333
14 Nov. 13	90	245	240	75	400	310	226.6666667
17 Nov. 13	135	260	125	130	200	350	200
20 Nov. 13	40	65	420	480	100	400	250.8333333
23 Nov. 13	245	475	100	20	340	410	265
26 Nov. 13	300	400	230	400	380	410	353.3333333
29 Nov. 13	155	385	310	240	260	400	291.6666667
Average	**138.3870968**	**145.645161**	**125.3225806**	**152.0967742**	**155.1612903**	**284.8387097**	**166.9086022**

Process capability, I Chart for individual and Run Chart with statistical summary for (31 samples) for coating solution , using the data collected in the control phase from the **Table 10** were done to assure the control phase process capability as shown in **Fig.13, 14, 15, 16**.

Table 11 showed that the Cp value 2.45 and the Cpk value 1.36 which indicated that, the process of bacterial count at coating solution is stable and capable after applying the improvement methodology. In additions, the mean value 284.84 for the bacterial count after improvement is less than the desired target 500 cfu/ ml. which means, the target was achieved. According to the calculation of Sigma Level using Z-Type method Cpk value 1.36 is an indication for Sigma Level value 4.2 with non-conforming PPM value 26.7082 so the current process Sigma Level after the improvement is 4.2 σ.

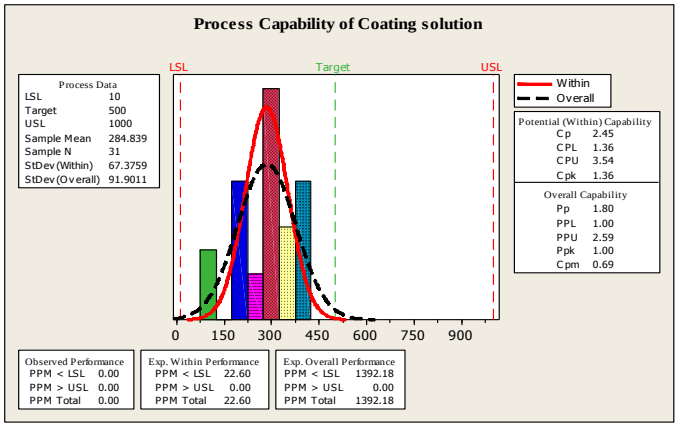

FIG.13: CONTROL PHASE PROCESS CAPABILITY

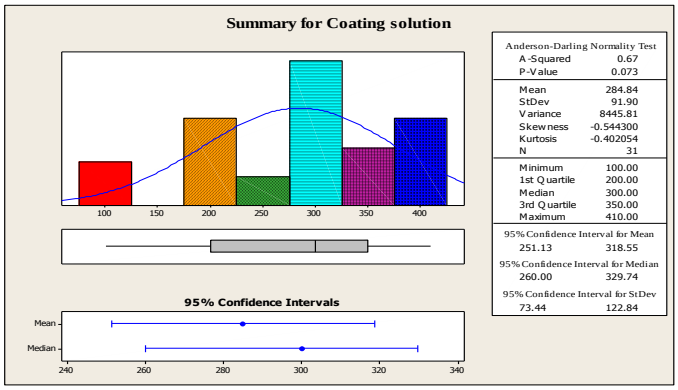

FIG.14: SUMMARY FOR COATING SOLUTION AFTER IMPROVEMENT

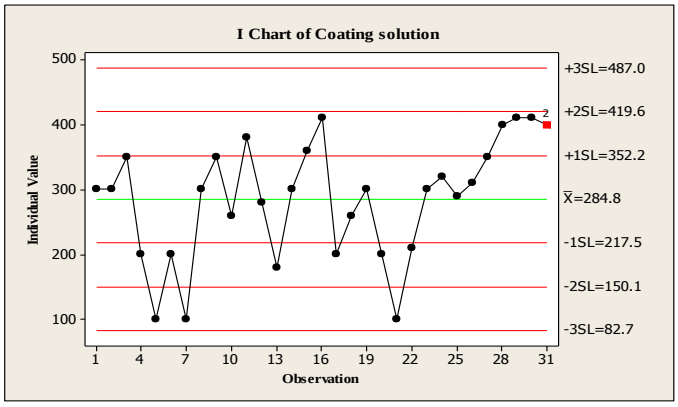

FIG.15: I CHART FOR BACTERIAL COUNT OF COATING SOLUTION AFTER IMPROVEMENT

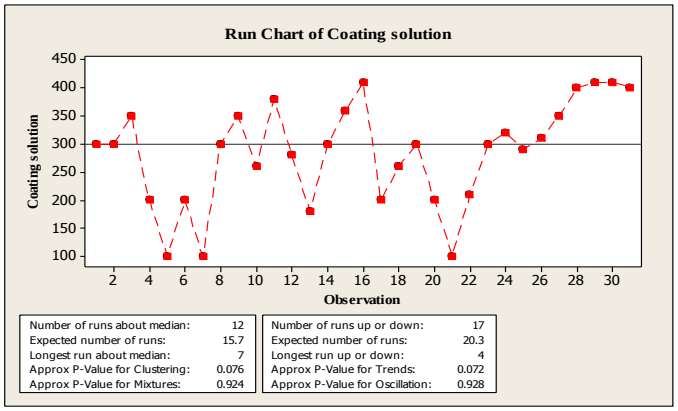

FIG.16: RUN CHART FOR BACTERIAL COUNT OF COATING SOLUTION AFTER IMPROVEMENT

TABLE 11: COLLECTED DATA FROM CONTROL PHASE PROCESS CAPABILITY

Standard deviation	166 CFU/ml
CP	2.45
Cpk	1.36
Mean value	284.84 CFU/ml
Target	500 CFU/ml
Approx. p-value for clustering	0.076 > 0.05
Approx. p-value for trends	0.072 > 0.05
Approx. p-value for mixtures	0.924 > 0.05
Approx. p-value for oscillation	0.928 > 0.05

TABLE 12: DATA COMPARISON BEFORE AND AFTER IMPROVEMENT AT BACTERIAL COUNT OF COATING SOLUTION

Observation	Before improvment	After improvement
Standard deviation	512 CFU/ml	166 CFU/ml
CP	0.18	2.45
Cpk	- 0.12	1.36
Mean value	1340.6 CFU/ml	284.84 CFU/ml
Target	500 CFU/ml	500 CFU/ml
Approx. p-value for clustering	0.991 > 0.05	0.076 > 0.05
Approx. p-value for trends	0.009 > 0.05	0.072 > 0.05
Approx. p-value for mixtures	0.768 > 0.05	0.924 > 0.05
Approx. p-value for oscillation	0.232 > 0.05	0.928 > 0.05

As illustrated in **Table 12,** we can clarify the following: The sample mean after the improvement took place was decreased from 1340.6 to 284.84, which mean that we reached the target 500 cfu/ml. The sample standard deviation after the improvement took place was decreased from 512 cfu/ml which considered a high value to 166 cfu/ml.. Variations in the control chart figure (17) before improvement took place have obviously-been eliminated in control chart **Fig. 18** which means, there are no points out of control.

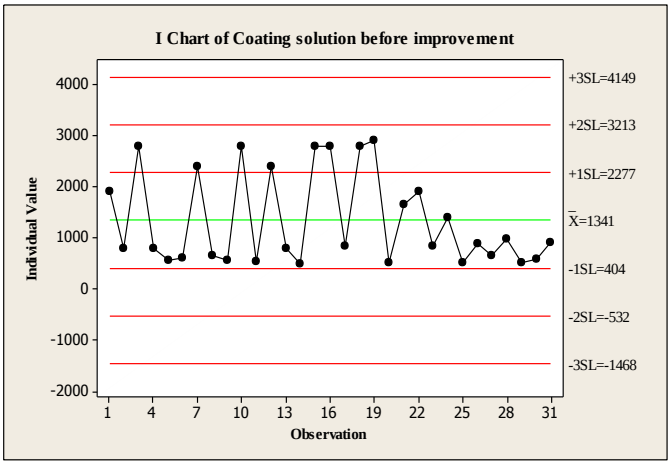

FIG.17: INDIVIDUAL I CHART FOR BACTERIAL COUNT BEFORE IMPROVING

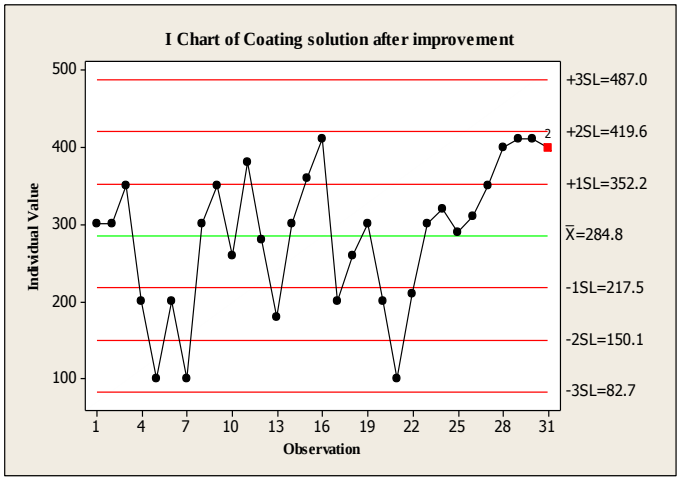

FIG.18: INDIVIDUAL I CHART FOR BACTERIAL COUNT AFTER IMPROVING

The approximate P values for Mixtures were-increased to be higher than 0.05 after improvement took place.

CONCLUSION: After identifying, the root causes of the bacterial count of coating solution, the Systematic use of the Six-Sigma Methodology through the research, ensured savings in terms of money and give safety (D.E.T) for patient.

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