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Application of Analysis of Variance for Vitamin B Injection Solution Defectives Reduction in the Pharmaceutical Industry

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Abstract

The objective of this research was to study the defectives reduction in the aseptic filling process in the pharmaceutical industry. The major nonconforming problem was the soot particles on the inner surface of vitamin B injection solution tube in the aseptic filling process. Analysis of Variance (ANOVA) was applied to determine factors, which had a significant effect on defectives percentage and the optimal levels of the factors to reduce defectives percentage. For experimental design, a Completely Randomized Design (CRD) was generated with 3 factors as follows: 1) needle type 2) needle position and 3) machine speed. According to the Analysis of Variance (ANOVA), needle type factor had a significant effect on defectives percentage. From the interval plot, the 95% confidence intervals of defectives percentage of vitamin B injection solution aseptic filling problem occurred by the two needle types were not overlapped. Therefore, the mean defectives percentage produced by the proposed type 1 needles was significantly less than the mean defectives percentage produced by the type 2 needles of the case study. Additionally, it was found that when the proposed type 1 needles were used, the mean defectives percentage was 4.25%. The mean defectives percentage of the current process using the type 2 needles was 15.90%. It can be concluded that when the proposed type 1 needles were used after the improvement, the mean defectives percentage decreased by 11.65%.

Keywords : Analysis of Variance; Design of Experiments; Defectives Reduction; Pharmaceutical Industry

Introduction

Waste management is a concept that focuses on the waste problems and includes different strategies to manage sustainably waste. These sustainable solutions include Refuse, Reduce, Reuse, Repurpose and Recycle. The 5R's Concept (Refuse-Reduce-Reuse-Repurpose - Recycle) is a sequence of steps on how to manage waste properly. **Refuse** can be explained as deny what is not needed, **reduce** refers to the reduction of wasteful and non-recyclable materials, and by reducing waste, we reduce production costs and avoid the unnecessary use of the resources such as materials, energy and water, **reuse** is about using again what is consumed, **repurpose** involves taking items that were meant for one purpose but can be used for other ones, and **recycle** is about turning something to a new product that might suffer a decrease in quality [1]. Refuse is the first step of the 5R process. It is the leading principle that urges us to refuse anything we don't really need; however, in this case study of a pharmaceutical company, vitamin B injection solution is the important product and it is necessary to treat a vitamin B deficiency. A deficiency in vitamin B can lead to various health problems, ranging from fatigue to permanent neurological problems. The top priority is Reduce, which is to reduce waste generation from the production process. Most of the production of waste should be reduced from the beginning. The main priority is always to reduce and prevent the waste generation from the manufacturing process (Reduce) [2]. The

objective of this research is to prevent the waste generation and reduce the percentage of defectives from aseptic filling process in the pharmaceutical industry. Vitamin B injection solution is the important product of the case study pharmaceutical company. Vitamin B helps our body use fat and carbohydrates for energy and make new protein. It is also important for normal blood, cells, and nerves. Most people get enough vitamin B in their diet, but a vitamin B deficiency may occur in certain health conditions such as poor nutrition, stomach/ intestinal problems, infection and cancer. Serious vitamin B deficiency may result in anemia, stomach problems, and nerve damage [3]. The nonconforming products data of the aseptic filling of vitamin B injection solution was collected and analyzed. It was found that the soot particles on the inner surface of vitamin B injection solution tube problem was the most important defectives problem.

According to the aseptic filling process of vitamin B injection solution, the Pareto chart was used to analyze and display in Figure 1 [4]. The most important nonconforming problem was the soot particles on the inner surface of vitamin B injection solution tube problem (90,879 tubes or 58.7%). The second major problem was the aseptic filling process contamination (39,069 tubes or 25.2%). There were 10,403 nonconforming tubes (6.7%) and 8,032 tubes (5.2%) occurred from vitamin B tube crack and seal leakage problems. Other defectives are 6,350 tubes (4.1%). According to the most important problem which was soot particles on the inner surface of vitamin B injection solution tube, the root cause was the inappropriate aseptic filling machine setup. Design of Experiments (DOE) was applied to the pharmaceutical industry in many case studies [5]. DOE was used to determine the optimal level of machine setup [6]. Analysis of Variance (ANOVA) was used for the study of the aseptic filling machine setup effects on the mean defectives percentage from the vitamin B injection solution aseptic filling process.

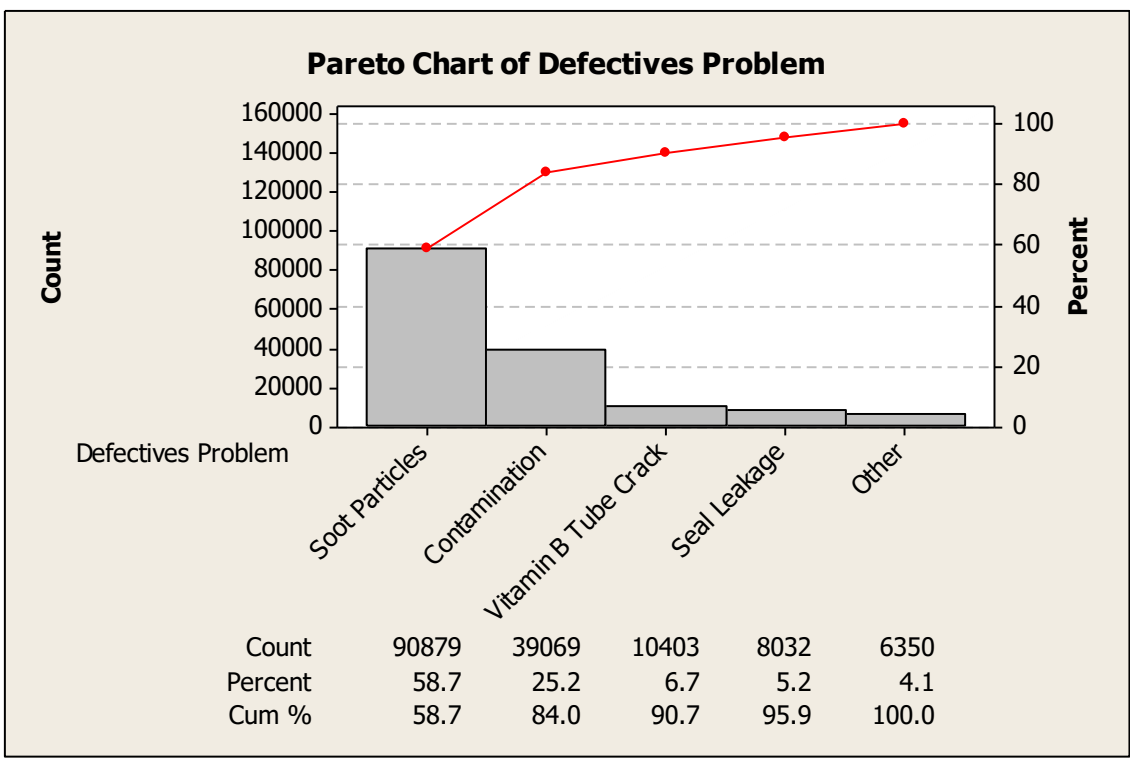

Figure 1 Pareto chart for nonconforming parts of the aseptic filling process in the case study pharmaceutical company

Methods

Design of Experiments (DOE) mathematical methodology used for planning and conducting experiments as well as analyzing and interpreting data was obtained from the experiments [7]. It was used for conducting scientific studies of a system, process or product in which input variables (Xs) were manipulated to investigate its effects on measured response variable (Y) [8]. Design of Experiments is statistical tool deployed in various types of system, process and product design, development and optimization. It has been a very useful tool traditionally used to improve product quality and reliability [9]. The usage of DOE has been expanded across many industries as part of decision making process along with a new product development, manufacturing process and improvement. It is not used only in engineering areas but it has also been used in administration, marketing, hospitals, plastic parts, food, pharmaceutical industry [10], energy, and architecture [11, 12]. Research work flow can be classified as follows:

1. State the objectives – it is a list of problems that are going to be investigated. In this research, Analysis of Variance (ANOVA) was used to study of aseptic filling machine setup effects on the mean defectives percentage of vitamin B injection solution in the aseptic filling process. The optimal level of machine speed, needle type, and needle position was analyzed and experimented.
2. Response variable definition – this is measurable outcome of the experiment that is based on defined objectives. The percentage of defectives from the vitamin B aseptic filling process was the response variable.
3. Determine factors and levels – selection of independent factors that have a significant effect on the response variable. To identify factors (machine speed, needle type, and needle position) that may affect the response variable (defectives percentage).
4. Determine Experimental Design type – a completely randomized design (CRD) was applied and planned.
5. Perform experiment using design matrix.
6. Analyze data - using the Analysis of Variance (ANOVA) statistical method.
7. Make conclusions and recommendations - using graphical representation of the results.

A Completely Randomized Design (CRD) of three factors experiment was applied for the optimization experiment. ANOVA was used for the analysis of factors (machine speed, needle type and needle position) affecting on the percentage of defectives. The type 2 needles were used before this research was conducted. Therefore, the unsuitable type of needles caused the soot particles on the inner surface of vitamin B injection solution tube problem. There were three machine speed levels, which were 8 pieces per minute, 10 pieces per minute, and 12 pieces per minute. There were two needle types including type 1 and type 2. The two needle position levels which were 0 mm and 3 mm above the vitamin B level in the vitamin B injection solution tubes were tested.

Results and Discussion

The experimenter should carefully choose a model before collecting data. The assumptions of ANOVA including normality, constant variance, and independence assumptions should be checked before the ANOVA is applied [13]. This is typically done by residual plots. Plots of residuals typically show trends more readily than plots of the response values [14]. Therefore, normality, constant variance, and independent assumptions were tested in the model adequacy checking as shown in Figure 2, Figure 3, and Figure 4.

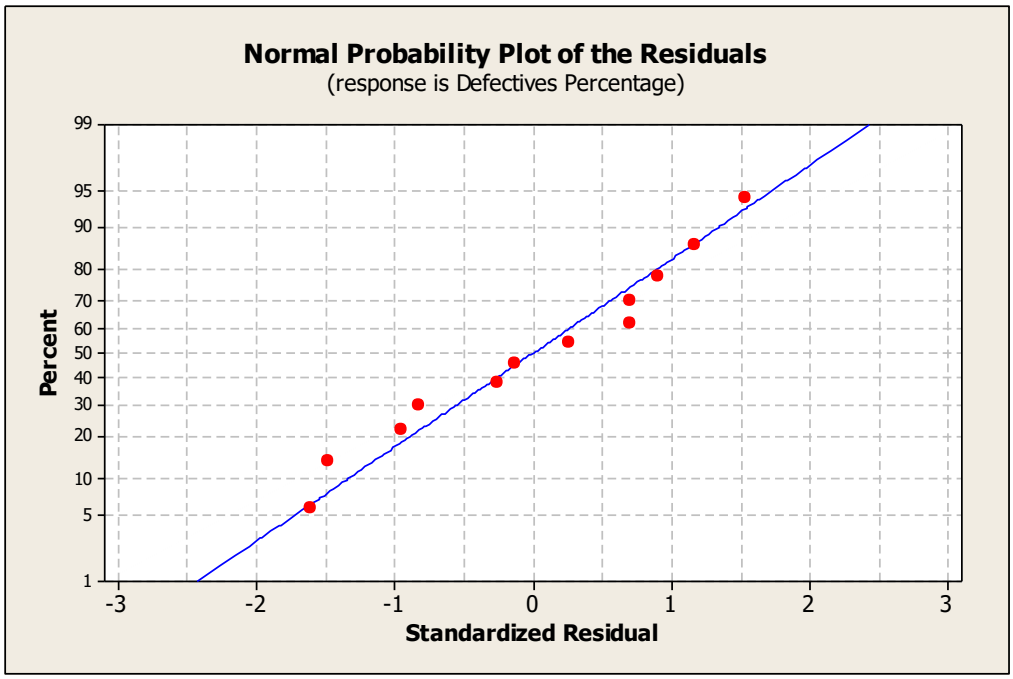

Figure 2 Normal probability plot of the residuals

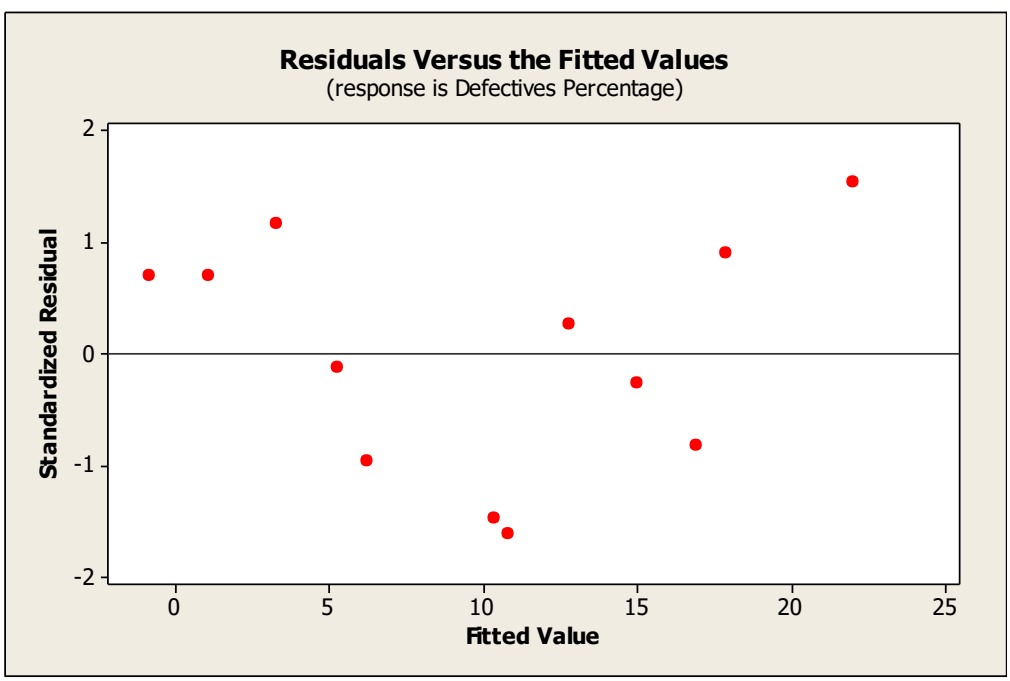

Figure 3 Constant variance assumption checking

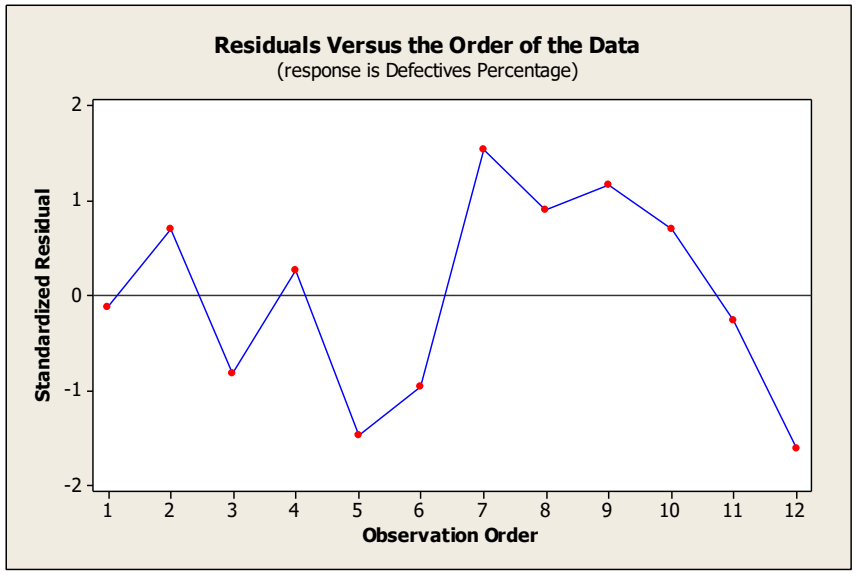

Figure 4 Residuals versus the order of the data (independence assumption)

According to the model adequacy checking [15], it was found that residuals were normally distributed. The variance of residuals was constant and the independence assumption was checked. Therefore, the ANOVA was suitable for the analysis of the three factors affecting on the mean percentage of defectives.

The needle type factor had a significant effect on the vitamin B injection solution aseptic filling mean defectives percentage since the p-value was 0.01, which was less than 0.05 significant level. The machine speed and needle position factors had no significant effects on the mean percentage of vitamin B injection solution nonconforming products as shown in Table 1.

Table 1 The ANOVA table for the experiment which defectives percentage was the response variable

General Linear Model: Defectives Percentage versus
Machine Speed, Needle Type, and Needle Position

Factor	Type	Levels	Values
Machine Speed	fixed	3	8, 10, 12
Needle Type	fixed	2	1, 2
Needle Position	fixed	2	0, 3

Analysis of Variance for Defectives Percentage, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Machine Speed	2	106.41	106.41	53.21	1.61	0.266
Needle Type	1	407.03	407.03	407.03	12.30	0.010
Needle Position	1	51.34	51.34	51.34	1.55	0.253
Error	7	231.56	231.56	33.08		
Total	11	796.34				

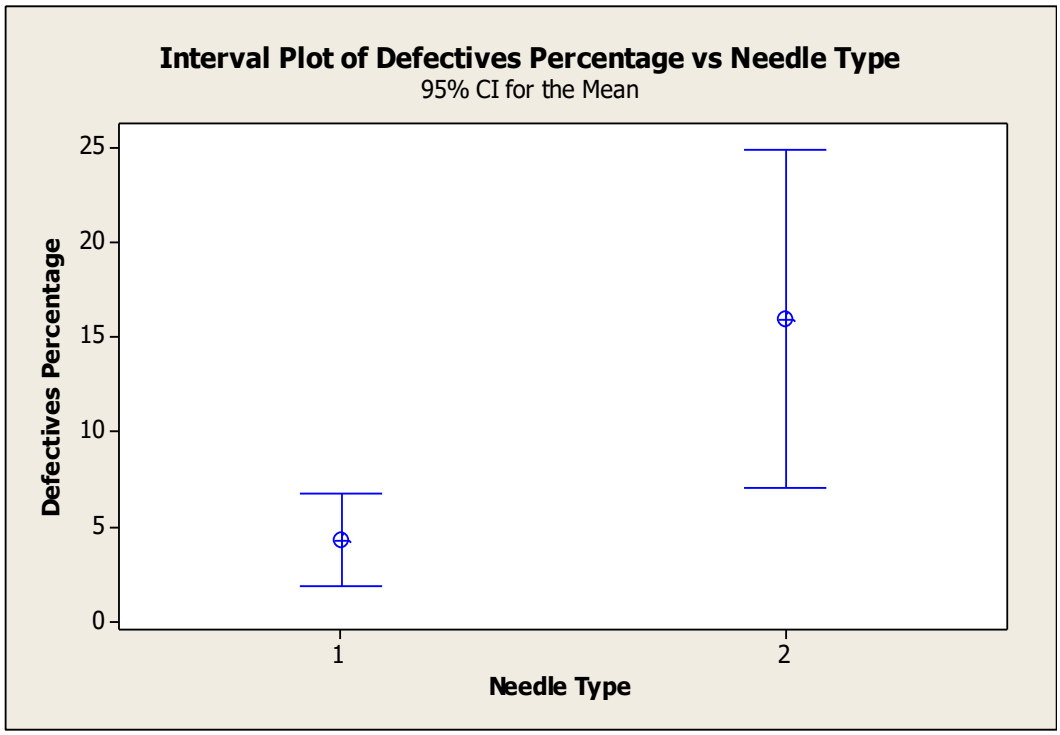

Figure 5 Interval plot of defectives percentage

Figure 5 displayed the interval plot of defectives percentage. From the interval plot, the lower and upper bounds of the 95% confidence interval for defectives percentage were 1.84% and 6.67% using the proposed type 1 needles. When the type 2 needles were used, the lower and upper bounds of the 95% confidence interval for defectives percentage were 6.96% and 24.84%. The two 95% confidence intervals for defectives percentage were not overlapped. Therefore, the mean defectives percentage produced by the proposed type 1 needles was significantly less than the mean defectives percentage produced by the type 2 needles of the case study.

Conclusions

The study of the defectives reduction in the aseptic filling process of the case study pharmaceutical company was conducted. Vitamin B injection solution tubes are the important products of the case study. The major nonconforming problem was the soot particles on the inner surface of vitamin B injection solution tube in the aseptic filling process. Experimental design was applied to determine the optimal level of aseptic filling machine setup for minimization of the mean percentage of defectives. The model adequacy checking was tested with the three assumptions, which are normality, equal variance, and independence assumptions. Analysis of Variance (ANOVA) was the appropriate statistical technique. For experimental design, a three-factor Completely Randomized Design (CRD) was generated and the ANOVA was carried out. According to the ANOVA table, it was found that the needle type had a statistically significant effect on the mean defective percentage. The appropriate needle type with the smaller value of the mean defective percentage was the type 1 needle. It was found that when the proposed type 1 needles were used, the mean defectives percentage was 4.25%. The mean defectives percentage using the type 2 needles was 15.90%. It can be concluded that when the proposed type 1 needles were used in the aseptic filling process of vitamin B injection solution after the improvement, the mean defectives percentage decreased by 11.65%. Further study about the inner diameter of tubes of vitamin B injection solution can provide the

opportunity to explore the vitamin B injection solution defectives reduction in the case study pharmaceutical company. The wide inner diameter tubes should be used to avoid the nonconforming problem in the aseptic filling process since the probability of the soot particles occurrence on the inner surface of vitamin B injection solution tube will be reduced significantly.

References

[1] Balwan W.K., Singh A. and Kour, S. 2022. 5R's of zero waste management to save our green planet: A narrative review. European Journal of Biotechnology and Bioscience. 10(1): 7-11.

[2] Asilahijani, H., Steiner, S.H. and MacKay, R.J. 2010. Reducing variation in an existing process with robust parameter design. Quality Engineering. 22: 30-45.

[3] Global Wellness Institute. 2022. Global Wellness Trends Report: The Future of Wellness 2022. New York.

[4] Bambharoliya, S.H. and Thakkar, H.R. 2015. Reducing rejection rate in small scale machining unit using 7 quality control tools - A Review. International Journal of Engineering Development and Research. 3(4): 582-586.

[5] Zhang, L. and Mao S. 2017. Application of quality by design in the current drug development. Asian Journal of Pharmaceutical Sciences. 12(1): 1-8.

[6] Yu L.X., Amidon G., Khan M.A., et al. 2014. Understanding pharmaceutical quality by design. AAPS Journal. 16(4): 771-783.

[7] Bisgaard, S. 1992. Industrial use of statistically designed experiments: Case study references and some historical anecdotes. Quality Engineering. 4: 547-562.

[8] Montgomery, D.C. 2019. Design and Analysis of Experiments. John Wiley & Sons Inc., New York.

[9] Goos, P. and Jones, B. 2011. Optimal Design of Experiments: A Case Study Approach. John Wiley & Sons Inc., New York.

[10] Yu, P., Low, M.Y. and Zhou, W. 2018. Design of experiments and regression modelling in food flavour and sensory analysis: A review. Trends in Food Science & Technology. 71: 202-215.

[11] Schlueter, A. and Geyer, P. 2018. Linking BIM and Design of Experiments to balance architectural and technical design factors for energy performance. Automation in Construction. 86: 33-43.

[12] Durakovic, B. and Torlak, M. 2017. Simulation and experimental validation of phase change material and water used as heat storage medium in window applications. Journal of Materials and Environmental Sciences. 8 (5): 1837-1846.

[13] Dean, A., Voss, D. and Draguljic, D. 2017. Design and Analysis of Experiments. Springer, New York.

[14] Montgomery, D.C. 2019. Introduction to Statistical Quality Control. John Wiley & Sons Inc., New York.

[15] Montgomery, D.C. and Runger, G.C. 2014. Applied Statistics and Probability for Engineers. John Wiley & Sons Inc., New York.