DESIGNING SETTING PARAMETER OF TABLET COMPRESSION PROCESS TO MINIMALIZE WEIGHT VARIATION

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ABSTRACT

Tablet weight is one of the most important quality characteristic in pharmaceutical industry to ensure tablet efficacious. Tablet compression process in one of the pharmacy manufacturer was found incapable for weight and has a high variability of weight from the target. This is because the optimum process parameter is not yet defined. This research implements Taguchi Method to design setting parameter of tablet compression process with one quality response; tablet weight. Two process factors are investigated, including machine speed (rpm) and filling volume (mm^3). This research adopted Taguchi's L_9 array to investigate the effects of the two process factors. To obtain the result, pareto anova and main effect analysis are implemented to determine the combination of optimal factor levels. As a conclusion, the optimum setting parameter is found at level 2 for both factors. The Cp value is improved from 0,82 to 1,34. While, the Cpk value is enhanced from 0,84 to 1,33.

***Keywords**: Tablet Compression, Taguchi Method, pareto anova, main effect*

1. INTRODUCTION

In the pharmaceutical industry, drugs are one of the major commodity that must be maintained in either quality, efficacy, or safety. To ensure supply of drugs that are safe, efficacious, and has the best quality, each pharmaceutical industry sets high standards to ensure that drugs are produced in accordance with the needs of the consumers.
Based on data from BKPM (Investment Coordinating Board) in 2012, there were more than 241 pharmaceutical manufacturer engaged in the pharmaceutical industry, which can be seen in Figure 1.

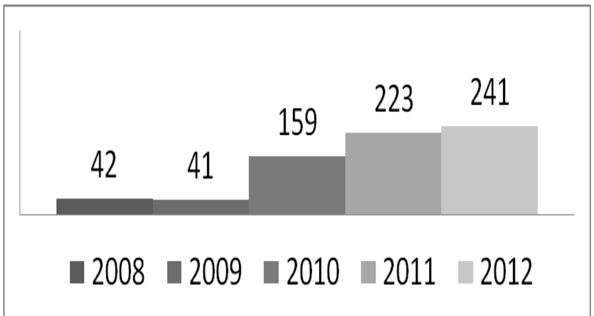

Figure **Error! No text of specified style in document.** . The growth of pharmaceutical manufacturer in Indonesia

(source: BPKM, 2012)

This is certainly become a concern for any manufacturer to be able to maintain and improve quality in order to survive in a tight competition. Quality, in the pharmaceutical industry, is defined as product specifications and its benefits to consumers. In fact, both of these cannot be separated, because the benefits of the product are related to the product specifications. The specification can be in the form of be weight, hardness level, dissolution times, thickness level, etc. The pharmaceutical manufacturer should be able to produce drugs that comply with the specifications that have been established, one of them is tablet weight (miligrams). Tablet specifications must be observed to ensure uniformity in the production, not only the appearance but also the therapy effect (b). In this research, tablet compression process was found incapable for weight in one of the pharmaceutical manufacturer in Indonesia. That is why it is necessary to conduct an experimental design to design and analyze the process parameters. The Taguchi method is widely applied because of its proven success in improving the quality of manufactured products in many business applications (a). That is why the utilization of

ISSN : 1978-774X

experimental design in the production process can support the process as a whole.

2. THEORETICAL BACKGROUND

The definition of quality is subjective according to the perspective of each person. According to Taguchi (j), quality is a loss incurred by the consumer due to the variation of product specifications. Losses can be caused by the variability of the function or side effects resulted by the product. According to Taguchi, variety is the main enemy in quality and every effort should be made to reduce the variation in the quality. Taguchi experimental design is extensively used as a tool to design a product to make it robust, which means insensitive to noise factors. According to Park (h), robust design is a quality engineering method that aims to optimize the quality of the product and process conditions, therefore the process is insensitive to various conditions that caused a decreasing in the quality. Taguchi method was first developed by a scientist from Japan named Dr. Genichi Taguchi in 1987. He was given the task to improve the telecommunications system in Japan. He used DOE theory to develop Taguchi method. Taguchi method focuses on making process and products robust to noise factors, for example by designing the process parameters. Parameters design are basically about determining the best combination of level and factors that affect the product or process (j). The design parameters steps are listed in the following (l):

1. Factors selection
2. Levels selection
3. Orthogonal Array Selection
4. Conduct experiments
5. Analyze results of experiments

3. METHODOLOGY

This research investigated tablet compression process of white film-coated tablets with a target weight of 300 mg (± 9 mg) with an oval shape. Tablet compression is done using a high-speed tablet compression machine, named JCMCO 2. Initial data collection was done by taking sample to calculate process capability that has been run using the help of Minitab 16 software. With the Cp value of 0,82 and Cpk value of 0,84, this tablet compression process found incapable. This means that the process has not been able to produce the tablet weight according to the specifications and has a large variation. Tablet compression process histogram is shown in Figure 2 .

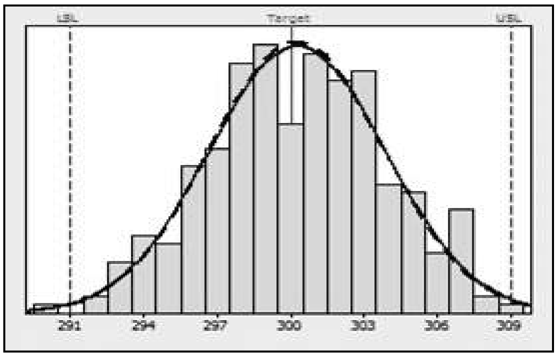

Figure 2. Initial histogram of tablet compression process

Design of experiment began with the selection of the necessary parameters to measure the quality characteristics, which in this case is the tablet weight (mg). The first phase of the Taguchi experimental design is to determine the influential factors and levels, which are shown in Table 1 and Table 2.

Table 1. Controllable Factors

Controllable Factors	Level 1	Level 2	Level 3
Filling volume (mm^3)	174,2	175,2	175,7
Machine speed (rpm)	41	43	45

Table 2. Noise Factor

Noise Factor	Level 1	Level 2
Granule Water Percentage	2,14%	2,17%

The next step was choosing an orthogonal array, which depends on number of factors and levels investigated in this research. In this study, there are two factors with three levels each. The calculation is done by determining the degrees of freedom to find

ISSN : 1978-774X

out minimum number of experiments need to be carried out, using equation 1 (k)

$$DOF = (nA-1)+(nB-1)+(nA-1)(nB-1) \quad (1)$$

Where nA is the number of levels of factor A and nB is the number of levels of factor B. Based on the calculation, the found out DOF is eight, which means eight number of experiments is enough to obtain enough informations. With three levels, two factors, and degress of freedom of eight, the orthogonal array of L_9 (3^2) is the most suitable one.

4. RESULT AND DISCUSSION

4.1. Data Collection

Data was collected with supervisors in accordance to the production schedule of the particular drug in this study. Experiments in the determined OA was conducted randomly. Each experiments took 100 tablets and then calculated the average value. The experimental results can be seen in Table 3. To calculate and analyze the data, we only use set data Y1 and Y3 .

After the results for each combination of factors and levels obtained, then next step us calculating S/N ratio to investigate the relationship between signal and noise using equation 2 (k)

$$Rasio S/N = 10\log_{10}\frac{(mean)^2}{\text{var}\,ians} \quad (2)$$

The calculation result of the S/N ratio is shown in Table 4 .

4.2. Pareto Anova

The calculation of Pareto ANOVA was done to see the contribution of each factor to the tablet weight variation. The calculation is done based on the value of S/N ratio and mean value. Pareto ANOVA for S/N ratio can be seen in Table 5 and Pareto ANOVA for mean value can be seen in Table 6. It can be seen that filling volume (mm^3) made a major contribution to the S / N ratio by 89 %. This means that this factor should be set at the optimal level to help lowering the varibilities .

4.3. Main Effect

To determine the optimal level of each factor, the calculation is of main effect need to be done, before plotted into a chart. Calculation of Main Effect for S/N Ratio obtained from the amount of factor A at level n (n = 1,2,3 ...) divided by the number of experiments using factor A at level (k). The results of the calculations for the Main Effect for S/N Ratio can be seen in Table 7, which is then plotted on a graph shown in figure 3 and 4. Can be seen from Figures 3 and 4, both factors give the S/N ratio at its maximal value at level two.

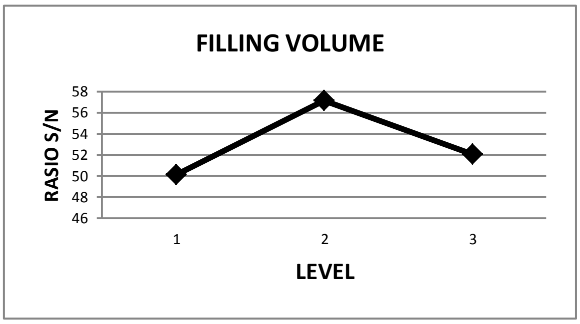

Figure 3. Filling volume *Main Effect* Plot for S/N Rasio

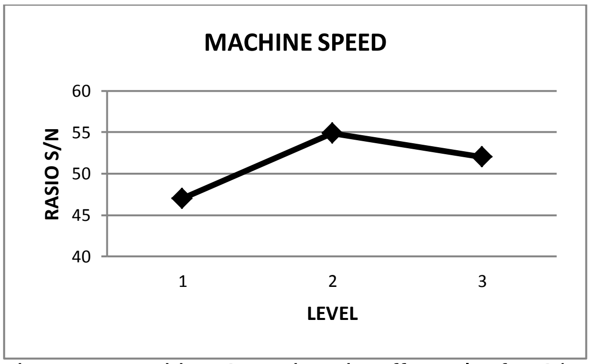

Figure 4. Machine Speed *Main Effect* Plot for S/N Rasio

Then, to determine the optimal level based on average values, the same steps were conducted, but the calculation is based on the mean value. The results of the calculation are shown in Table 8, which was then plotted on a graph shown in Figure 5 and 6. Can be seen from Figure 5 and 6, the filling volume factors is optimal when it sets at level three and machine speed at level two .

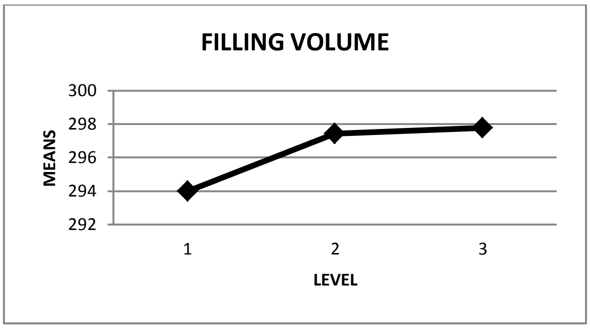

Figure 5. *Filling volume Main Effect* Plot for Mean Value

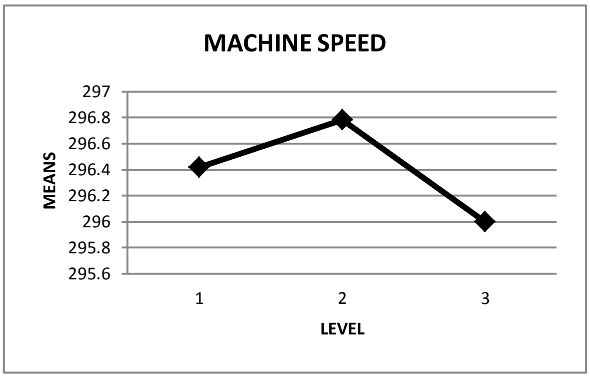

Figure 6. *Machine speed Main Effect* Plot for Mean Value

4.4. Suggested Parameter

Based on the Pareto ANOVA and main effects, it can be seen that there is a difference for filling volume, which for S / N ratio should be set at level two, but for the mean value should be set at level three. To overcome this, we can refer back to Table 5, which is based on the calculation of Pareto ANOVA, filling volume is more significant on the S / N ratio (by 89 %), therefore to determine the optimal level for filling volume, use the calculation based on analysis of the main effect S/N ratio, which is on the level two. While, the optimal level of machine speed is on level two.

4.5. Predicting S/N Ratio

After obtained the optimal setting parameters of tablet compression process, the value of the S/N ratio is predicted. Predicted value of S/N ratio is obtained from the calculation of any effect of the optimal level of each parameter. The calculation using equation 3 (I)

$$RasioS / N = T + (DS_2 - T) + (MS_2 - T) \qquad (3)$$

Where, T is the average value of the S/N ratio from the overall results of the experiment, DS_2 is the average value of the S/N ratio for filling volume at the level 2 and MS_2 is the average value of the S/N ratio for machine speed at the level 2. By using the above equation, the predicted value of S/N ratio is equal to :

Predicted S / N ratio = 60.70863589 db

4.6. Parameter Testing

The combination of parameters that have been determined will be tested by calculating process capability using data on a data set Y2 and Y4 from Table 3. Cp and Cpk calculation is done by using Minitab 16 software. From the calculation, the value of Cp and Cpk process is 1,34 and 1,33 respectively. This means that the process is capable of producing the appropriate specifications. Histogram of this testing can be seen in Figure 7.

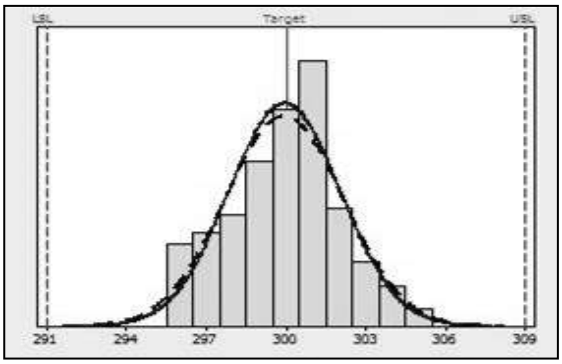

Figure 7. Tablet Compression Process Testing Histogram

5. CONCLUSION

Initially, the process was found capable for weight. To improve the performance of this process, this research aims at getting the optimal parameter of tablet compression process.

The main factors studied are machine speed and filling volume using the L_9 array. Then, the pareto anova and main effect are employed to identify the combination of optimal factor levels, which is found as at the level 2 for each factor. The Cp value is improved from 0,82 to 1,34. While, the *Cpk* value for is enhanced from 0,84 to 1,33. Future research may uncover parameter design for more than one quality characteristics of tablet, such as hardness level, dissolution times, etc.

6. REFERENCE

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Table 3. Experiment Result

Experiment Number	Inner Array		Outer Array			
	A	B	Water Percentage 2,14%		Water Percentage 2,17%	
	Filling volume (mm^3)	*Machine speed* (rpm)	Tablet Weight (mg)			
			Y1	Y2	Y3	Y4
1	1	1	295.57	300.51	291.89	296.17
2	1	2	296.49	297.42	292.51	295.76
3	1	3	295.7	297.32	291.85	295.68
4	2	1	300	299.46	295.98	297.61
5	2	2	298.92	300.48	297.35	299.7
6	2	3	296.85	298.7	295.48	298.96
7	3	1	299.93	301.5	295.15	294.93
8	3	2	299.11	301.62	296.31	296.65
9	3	3	300.4	300.97	295.73	298.13

Table 4 S/N Ratio Calculation

Experiment Number	Rasio S/N (db)
1	50.82943178
2	49.47529767
3	50.07111632
4	49.37921496
5	60.45390457
6	60.36062272
7	40.79458264
8	54.56811295
9	44.36316574

Table 5. Pareto Anova for S/N Ratio

FAKTOR		*Filling volume*	*Machine speed*	
Sum at Factor Level	1	148.925629	141.0032294	
	2	162.9091099	164.4973152	
	3	98.93127868	156.0949048	
SS of difference		6788.135691	850.3312343	
DOF		2	2	
SS/DOF		3394.067846	425.1656172	3819.23
Contribution Ratio		0.888677762	0.111322238	1
Percent Contribution		**89%**	**11%**	

Table 6.Pareto Pareto Anova for Mean Values

FAKTOR		*Filling volume*	*Machine speed*	
Sum at Factor Level	1	882.005	889.26	
	2	892.29	890.345	
	3	893.315	888.005	
SS of difference		2667.61	2667.61	
DOF		2	2	
SS/DOF		1333.805	1333.805	2667.61
Contribution ratio		0.5	0.5	1
Percent Contribution		**50%**	**50%**	

ISSN : 1978-774X

Table 7. *Main Effect* for S/N Ratio

	LEVEL		
FAKTOR	1	2	3
Filling volume	50.12528192	57.1646	52.03163493
Machine speed	47.00107646	54.8324	52.03163493

Table 8 *Main Effect* for Mean Value

	LEVEL		
FACTOR	1	2	3
Filling volume	294.0017	297.43	297.7717
Machine speed	296.42	296.7817	296.0017