International Journal of Emerging Engineering Research and Technology
Volume. 2, Issue 6, September 2014, PP 64-71
ISSN 2349-4395 (Print) & ISSN 2349-4409 (Online)

Simulation and Optimisation of a Pharmaceutical Production Line

Pramod Kumar[1], Aravind S[2], Mathew Samuel[3]

[1]Assoc. Professor, Dept. of Mechanical Engineering, Viswajothi College of Engg., Ernakulam, India
[2]Asst. Professor, Dept. of Mechanical Engineering, Viswajothi College of Engg., Ernakulam, India
[3]PG student, Dept. of Mechanical Engineering, Viswajothi College of Engg., Ernakulam, India

Abstract: *Pharmaceutical companies are allowed to deal in generic or brand medications and medical devices. Thus it is essential that the product conforms to specified customer requirements. In order to analyse the performance of the process, the critical factors which influence the production are evaluated. The objective of the study is to simulate the pharmaceutical production line using ARENA software and optimize the line by Design of Experiments technique in MINITAB by considering the response factor 'work in progress'. The critical factors identified are batch size, transfer time and the number of resources. A Taguchi approach is employed to gather experimental data. Then, based on signal-to-noise (S/N) ratio, the best sets critical parameters have been determined. Using these parameters values, the 'work in progress' may be minimized.*

Keywords: *simulation, optimization, signal to noise ratio, Taguchi method, analysis of variance*

1. INTRODUCTION

The quality of health care is very important to any society. The drugs obtained from the pharmacy prescribed by the physician are expected to cure the infection or relieve the pain and have its intended effect. People expect that the bottle of medicine has the specified number of tablets and that each tablet contains the specified quantity of the correct drug.

A number of unit processes are involved in making tablets, including particle size reduction and sizing, blending, granulation, drying, compaction, and (frequently) coating. Various factors associated with these processes can seriously affect content uniformity, bioavailability, or stability. Factors affecting the production line effectiveness of pharmaceutical companies include the different processes, operators, batch size, transfer time etc. There are different productivity improvement opportunities for the company by altering the above factors.

From the study conducted at a pharmaceutical company, it is evident that the production line is almost perfect but there exists a slightly higher work in progress items (larger numbers in queue). The ultimate objective of this study is to reduce the work in progress by finding out the optimised levels of the critical factors. To identify the various improved methods, the production line is modeled using Arena simulation software and to further improves the productivity by minimising the work in progress, the production line is optimised using Taguchi Design of Experiments.

Simulation, optimization and production improvement form an integrated part of modern engineering and industry. Now it has become the favourite area of today's research community. Some of the recent works in the field of simulation and optimisation are mentioned here.

Ritesh N. Sharma, mentioned in his paper that the optimization techniques are abundant in pharmaceutical industry. In general, all the required information should be obtained from as few experiments as possible. Conventional techniques such as response surface models or simplex optimization are often used. With the advent of the computer in the laboratory, a new class of optimization problems arose which could not be tackled with the standard methodologies [1]. Nilay Shah in 'Pharmaceutical supply chains: key issues and strategies for optimisation 'describes that supply chain optimisation is now a major research theme in process operations and management. A great deal of research has been undertaken on facility location and design, inventory and distribution planning, capacity and production planning and detailed scheduling and directly addresses the issues faced in the pharmaceutical sector. On the other hand, this sector is very much ready for and in need of sophisticated supply chain optimisation techniques [2]. Stuart C. Porter, Richard P. Verseput, and

Charles R. Cunningham, The use of design of experiments (DOE) software and methods allowed the authors to quantify the effects of changes in coating process conditions on the quality and performance of film-coated tablets. The application of DOE has the potential to allow rapid optimization of coating performance in a wide range of customer application environments to meet changing customer needs [3]. Prameth Tantivanich suggested a simulation approach for productivity improvement of an IC factory**.** It is used to develop a simulation model to intimate a real world IC assembly line in order to identify alternatives for productivity improvement. The model is developed under ARENA simulation software. Simulation methodology has been conducted to verify and validate the model before applications to the study [4]. K. H. Al-Khafaji et.al, conducted a study of production improvement by using lean with simulation modeling. The aim of this research is to study the effect of the shift from the traditional style of production to the application of modern techniques of lean in one of the old Iraqi industries to improve the flow of production and demand processing by reducing line intersections with optimal usage of available facilities [5].

Mandenius and Carl-Fredrik wrote 'Quality by Design (QbD) for biotechnology-related Pharmaceuticals'. The aim of the paper is to provide an update on the present status of using QbD in biotechnology-related applications in the pharmaceutical industry. The report summarizes the essential parts of the presentations and covers the industrial, academic, and regulatory aspects of QbD. It concludes with recommendations for further work and development.[6]. Torbjorn Lundstedt, Elisabeth Seifert published 'Experimental design and optimization'. The aim with this tutorial is to give a simple and easily understandable introduction to experimental design and optimization. The screening methods described in the paper are factorial and fractional factorial designs. Identification of significant variables are performed by normal distribution plots as well as by confidence intervals [7]. G. Kutz, T. Walger, 'Optimisation of a Film Coating Process using Design of Experiments' Tablet coating is a process with manifold critical process parameters. The wide range of coating conditions - operating parameters, equipment, configuration options - has a profound consequence interms of development of robust coating processes. Goal of this work was to quantitatively define the effects of critical process parameters on coating quality [8]. L. Savadamuthu et al mention that the proposed quality improvement methodology caused significant reductions in the defect rate in a very short period of time. This reduction in defects implies that the selected tools such as the orthogonal array, the signal-to-noise ratio and analysis of variance are suitable for establishing- the required improvement [9]. Kundan Kumar et al suggest that traditional optimization techniques have very limited scope because of the complexity of the problems since they require a very large number of experiments But Taguchi Technique requires very less number of experiments to optimize quality characteristics [10]. Eugenie Khlebnikova in the paper 'Statistical Tools for Process Qualification' discusses statistical tools that can be used to analyze process validation data. It covers descriptive statistics, control charts, process capability, and tolerance intervals. The requirement for statistical analysis is driven by the US Food and Drug Administration's Guidance for Industry Process Validation: General Principles and Practices, which emphasizes that the process validation data should be statically analyzed in order to gain full understanding of the manufacturing process and its variation [11].

2. SIMULATION MODEL

Various unit processes are involved in making tablets, including particle size reduction and sizing, blending, granulation, drying, compaction, and (frequently) coating. Various factors associated with these processes can seriously affect content uniformity, bioavailability, or stability.

Content uniformity is the degree of consistency in the amount of the drug substance among dosage units. Multiple capsules or tablets are selected at random and a suitable analytical method is applied to assay the individual content of the active ingredient in each capsule or tablet.

Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action. Bioavailability of a drug is largely determined by the properties of the dosage form, which depend partly on its design and manufacture. Differences in bioavailability among formulations of a given drug can have clinical significance; thus, knowing whether drug formulations are equivalent is essential.

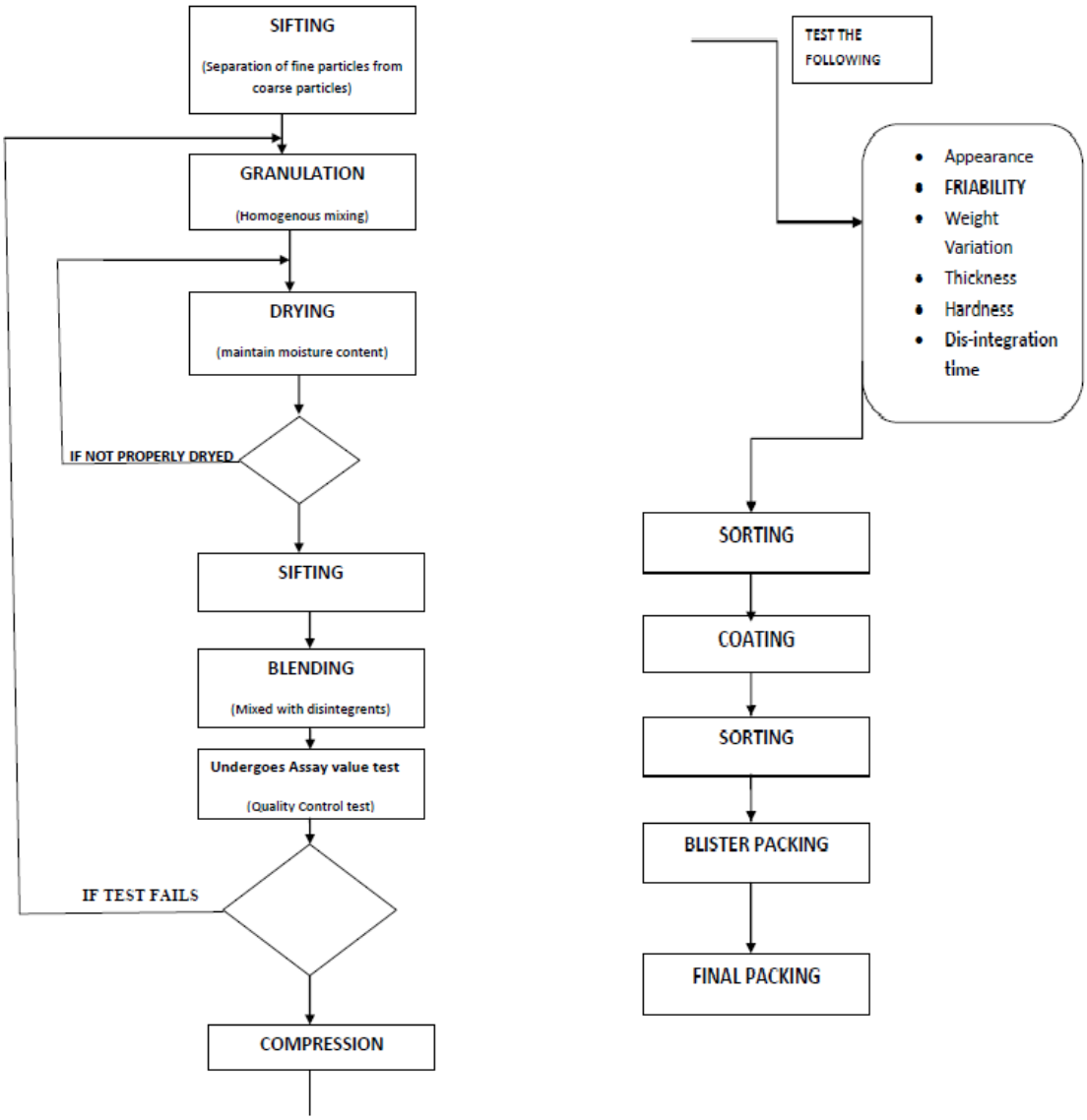

Fig1. *Process flow chart*

The different processes involved are:

2.1. Sieving

In this step, fine particles are separated from coarse particles in order to attain a uniform particle size. In manufacturing of compressed tablet, the mixing or blending of several solid ingredients of pharmaceuticals is easier and more uniform if the ingredients are approximately of same size.

2.2. Granulation

A Rapid Mixer Granulator (RMG) is employed in manufacturing tablets. It helps in homogenous mixing and controlled granule size.

2.3. Drying

Drying is a most important step in the formulation and development of pharmaceutical product. It is important to keep the residual moisture low enough to prevent product deterioration and ensure free flowing properties. The equipment used is Fluid Bed Dryer. After drying, the mixture undergoes sieving to obtain fine particle size.

2.4. Blending

The powdered granules are blended well with the disintegrants at an optimum mixing time and speed. After blending, the mixture undergoes quality test known as the Assay value test, where the content of the active ingredient is analysed. Once it passes the test, the mixture moves to the next step.

2.5. Compression

In this stage, the mixture is being compressed to get the final product. It 'squeezes' the ingredients into the required tablet shape with extreme precision. Each tablet is made by pressing the granules inside a die, made up of hardened steel.

2.6. Sorting

The tablets are sorted and broken tablets and other defective tablets are removed and sent for packaging.

2.7. Packaging

Blister packaging is employed for tablets before it is being sent for distribution.

The model developed in Arena software corresponding to the process flow is shown in the Figure 2

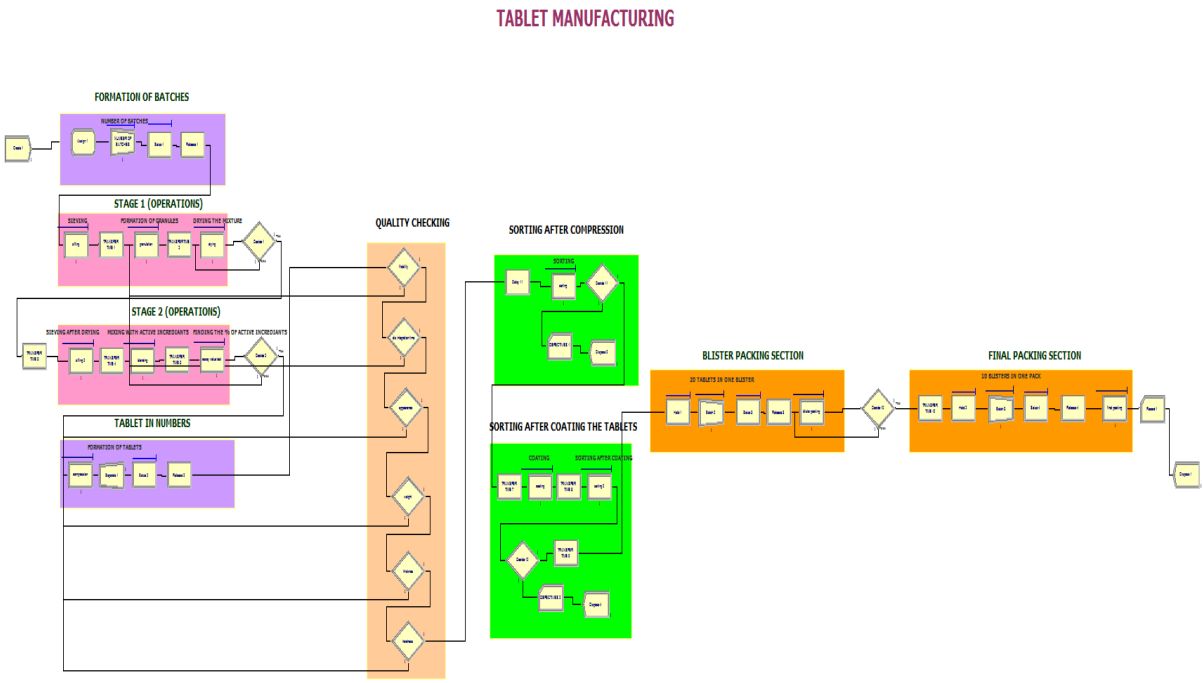

Fig2. *Model developed in Arena*

3. EXPERIMENTAL DESIGN

The different factors which influence the production are identified on discussion with experts and the most critical factors among them are prioritised for optimising the production line. The critical factors are batch size, transfer time and the number of resources. There are different productivity improvement opportunities for the companies by altering the above factors. The limits of values at the three levels are found out by expert opinion. Later on trial and error method the values for the three critical factors are fixed. The experiments were carried out with three factors at three levels each, as shown in Table 1. The fractional factorial design used is a standard L_{27} orthogonal array. This orthogonal array is chosen due to its capability to check the interactions among factors. The response factor is the work in progress (WIP) in numbers. The Table 2 shows the orthogonal array (L27) experimental design, input and output (response) parameters.

Table1. *Factors and Levels*

Factors/ Levels	A Batch size (No.)	B Transfer time (minutes)	C Number of resources (No.)
1	5000	18	19
2	10000	32	25
3	25000	54	14

Table2. *Orthogonal array with response factor*

Expt. No.	Batch size	Transfer time	Number of resources	Work in progress (WIP)	Expt. No.	Batch size	Transfer time	Number of resources	Work in progress (WIP)
1	1	1	1	738	15	2	2	3	715
2	1	1	2	734	16	2	3	1	734
3	1	1	3	740	17	2	3	2	734
4	1	2	1	710	18	2	3	3	737
5	1	2	2	706	19	3	1	1	705
6	1	2	3	726	20	3	1	2	704
7	1	3	1	728	21	3	1	3	708
8	1	3	2	730	22	3	2	1	704
9	1	3	3	730	23	3	2	2	703
10	2	1	1	721	24	3	2	3	705
11	2	1	2	718	25	3	3	1	706
12	2	1	3	725	26	3	3	2	708
13	2	2	1	712	27	3	3	3	710
14	2	2	2	712					

4. RESULTS AND DISCUSSION

4.1 Optimum Values of Critical Parameters Based on Signal to Noise Ratio

As per the Taguchi's L_{27} array there are 27 different experiment setups with the factors at different levels. These different setups are made run in simulation software Arena and the performance measure (WIP) value of each run are recorded. The software used to analyse the optimum levels is Minitab (Version 17). The S/N ratio values of the rejection are calculated, using the smaller the better characteristics:

$S/N = -10 \log (\Sigma y2)/n$

n - Number of experiments in each set up.

y – Work in Progress which is the response.

The signal to noise ratio corresponding to each experimental set is obtained. The optimum condition is that of larger signal to noise ratio (Table 3).

Table3. *Response Table*

Level	Batch size (A)	Transfer time (B)	Number of resources (C)
1	-57.23	-57.16	-57.12
2	-57.18	**-57.03**	**-57.10**
3	**-56.97**	-57.19	-57.17
Delta	0.25	0.17	.06
Rank	1	2	3

The levels of optimum condition are **A3 B2 C2.** That is batch size at level 3, transfer time at level 2 and number of resources at level 2.

4.2 Analysis of Results of Optimisation

Analysis of variance (ANOVA), a statistical approach is used for interpreting experimental data. With ANOVA, interaction between different parameters can be evolved and helps to find out the average performance difference of the parameters. The intention of ANOVA is to show the variation of each factor with respect to the total variation observed in the result. The lowest response value will be classified by the main effect plots identified from each level. With ANOVA, Significant and non significant factors are identified which helps to minimise the response factor.

The input parameters were optimized by using ANOVA for determining the optimal critical parameters with the consideration of multiple performance characteristics and finally verified. Table 4 shows the ANOVA table for Work in Progress as a function of critical parameters (batch size, transfer time and number of resources). From the ANOVA tables, the optimal critical parameters setting can

be obtained by considering minimum Work in Progress (WIP). Furthermore, this approach is feasible to obtain optimal critical parameters for a minimum Work in Progress by Analysis of Variance.

Table4. ANOVA *table for Work in Progress (WIP)*

Source	DF	Seq SS	Adj SS	Adj MS	F	% Contribution
Batch size	2	0.329783	0.329783	0.164892	97.51	54.46412
Transfer time	2	0.139597	0.139597	0.069799	41.27	23.05464
Number of resources	2	0.020195	0.020195	0.010098	5.97	3.33523
Batch size*transfer time	4	0.092116	.092116	0.023029	13.62	15.21308
Batch size*Number of resources	4	0.004353	0.004353	0.001088	0.64	0.718904
Transfer time*Number of resources	4	0.005932	0.005932	0.001483	0.88	0.979696
Residual Error	8	0.013529	0.013529	0.001691		2.23433
Total	26	0.605505				

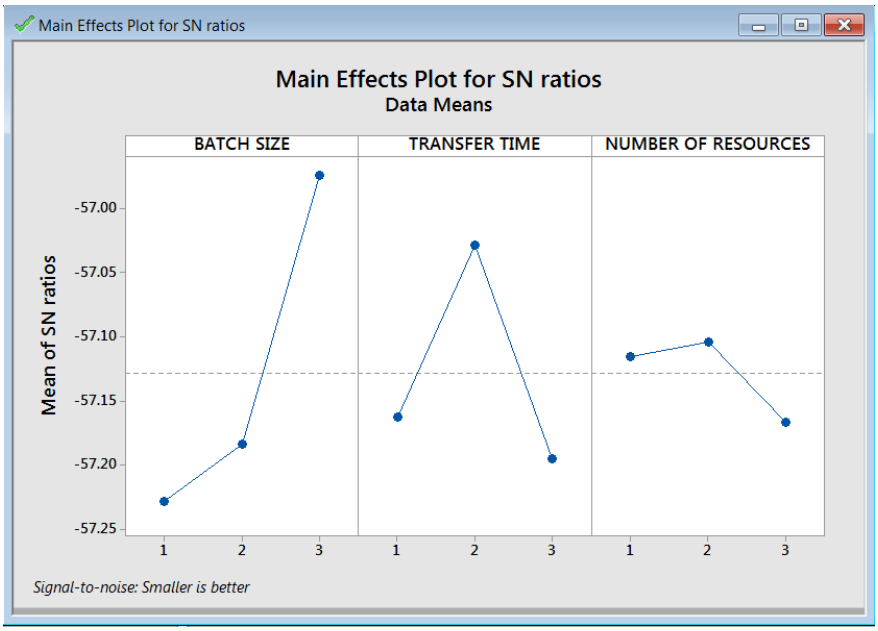

Fig3. *Main Effects Plot for S/N ratios*

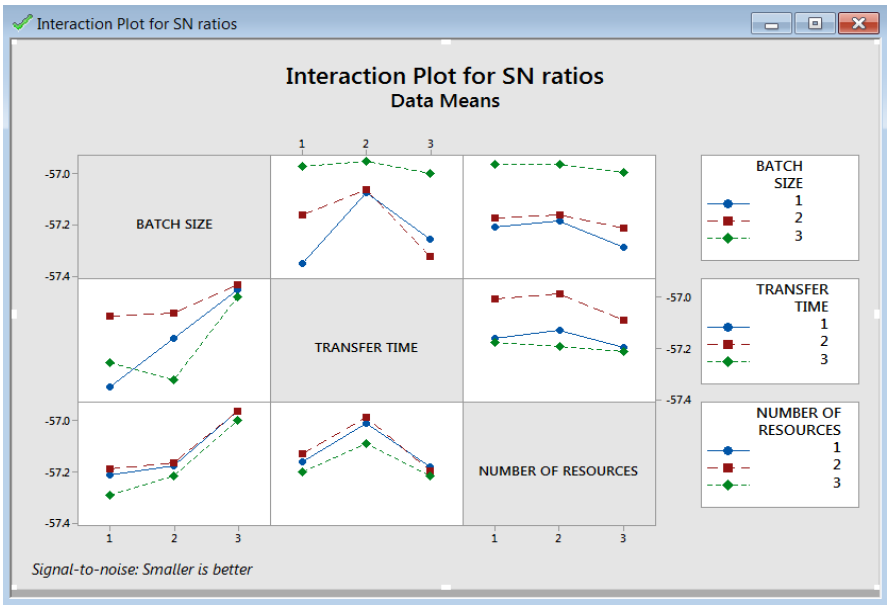

Fig4. *Interaction plot for S/N ratios*

Effect of Critical Parameters on Work in Progress (WIP)

Main Effects Plot (Figure 3) gives the plot of data means when multiple factors are present in the experiment. The points in the plot are the means of the response variable at the various levels of each factor, with a reference line drawn at the grand mean of the response data. Main effects plots are used for comparing magnitudes of main effects. The main effects plot displays the response means for each factor level in sorted order if the factors are numeric. The effects are the differences between the means and the reference line.

From the graphs obtained, observations show that the value of WIP shows an increasing trend towards batch size of level 1, 2 and 3. In case of transfer time, the trend increases from level 1 to level 2 while trend decreases for level 3. Number of resources shows almost same trend of transfer time. The optimum values are for higher signal to noise ratios. That is batch size at level 3, transfer time at level 2 and number of resources at level 2.

The data for analysis of variance shows that the values are significant for batch size and transfer time. It means that the batch size and transfer time influences significantly on the rejection value at a significant level of 0.05. The batch size and transfer time have a contribution for the rejection 54.46412% and 23.05464% respectively. From this result, it can be concluded that the batch size is more significant and give most contribution to the Work in Progress (WIP). Determining an optimal batch quantity in a production system has been the primary focus recently among the researchers since the batch size has a significant influence in the production process.

Interactions plots (Figure 4) are useful for judging the presence of interaction. Interaction is present when the response at a factor level depends upon the level(s) of other factors. Parallel lines in an interactions plot indicate no interaction. The greater the departure of the lines from the parallel state, the higher the degree of interaction. To use interactions plot, data must be available from all combinations of levels.

5. CONCLUSION

Work in Progress (WIP) refers to all materials and partly finished products that are at various stages of the production process. WIP excludes inventory of raw materials at the start of the production cycle and finished products inventory at the end of the production cycle. The critical parameters which influence the production are optimised for minimum value of Work in Progress.

Taguchi's L_{27} orthogonal array in Design of Experiments is taken for optimising the critical factors. Work in progress is taken as the response/performance factor. Taguchi method is a powerful tool which can offer simultaneous improvements in performance factors. Optimisation using Design of Experiments is done with the software MINITAB (version 17).

From the study it can be inferred that:

- Taguchi's Design of Experiments method is suitable to optimise the production line.
- The optimum levels of the critical parameters where the work in progress is minimum are:

Table5. *Optimum levels of critical parameters*

Batch size (numbers)	Transfer time (minutes)	Number of resources (numbers)
25000 (Level 3)	32 (Level 2)	25 (level 2)

REFERENCES

[1] Ritesh N. Sharma (2011) 'Optimization techniques in pharmaceutical industry: A Review'Journal of Current Pharmaceutical Research 2011; 7 (1): 21-28

[2] Nilay Shah (2004) 'Pharmaceutical supply chains: key issues and strategies for optimisation' Computers & Chemical Engineering 01/2004; DOI: 10.1016/j.compchemeng.2003.09.022

[3] Stuart C. Porter, Richard P. Verseput, and Charles R. Cunningham 'Process Optimization Using Design of Experiments' October 1997, pharmaceutical technology.

[4] Prameth tantivanich et.al 'a simulation approach for productivity improvement of an IC factory' Bangkok : King Mongkut's University of Technology Thonburi, 2002 (T E16915)

[5] K. H. Al-khafaji, M. R. Al-rufaifi –"A case study of production improvement by using lean with simulation modeling",2012.

[6] Mandenius, Carl-Fredrik (2009) 'Quality by Design (QbD) for biotechnology-related Pharmaceuticals'. Biotechnology journal

[7] Torbjorn Lundstedt , Elisabeth Seifert (1998) 'Experimental design and optimization'

[8] G. Kutz, T. Walger (2006) 'Optimisation of a Film Coating Process using Design of Experiments' University of Applied Sciences, Detmold, Germany

[9] L. Savadamuthu, S. Muthu, P. Vivekanandan in their paper Quality Improvement in Turning Process using Taguchi 's Loss Function, (2011)

[10] Kundan et al, 'Optimal Material Removal and Effect of Process parameters of Cylindrical Grinding Machine'International Journal of Advanced Engineering Research and Studies EISSN2 249–8974

[11] Eugenie Khlebnikova (2012) 'Statistical Tools for Process Qualification' Early Childhood Education, Ohio University, Zanesville, USA Human Ecology, Youngstown State University.

AUTHORS' BIOGRAPHY

Dr. Pramod Kumar is working as Associate Professor in the Department of Mechanical Engineering at Viswajyothi College of Engineering, Vazhakulam since 2011. He received PhD in Mechanical Engineering from Delhi University in 2010 and areas of interest include simulation, Industrial management, flexibility, productivity.

Mr. Aravind S is working as Asst Professor in the Department of Mechanical Engineering at Viswajyothi College of Engineering, Vazhakulam since 2011. His specialization is in Production and Industrial Engineering and areas of interest include optimization, Supply Chain management, Mathematical Modeling and simulation, Genetic Algorithms.

Mr. Mathew Samuel is persuing M.Tech (Industrial Engineering and Management) at Viswajyothi College of Engineering and Technology, Ernakulam. He had taken B.Tech from College of Engineering, Adoor affiliated to Cochin University of Science and Technology. Areas of interest include simulation, optimisation.