DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(12), 1461-1477 (1993)

TABLET FORMULATION : GENICHI TAGUCHI'S APPROACH

A.M. DIEMUNSCH (*) , J.Y. PABST (**)
C. CONSTANT (***), C. MATHIS (*) and A. STAMM (**)

(*) Laboratoire de Pharmacie Galénique
Université Louis Pasteur – Strasbourg
67401 – ILLKIRCH (France)

(**) Laboratoire de Pharmacotechnie
Université Louis Pasteur – Strasbourg
67401 – ILLKIRCH (France)

(***) Peugeot SA
123, Avenue Félix Faure
75015 PARIS (France)
and
Université de Compiègne (France)

ABSTRACT

In this paper the Taguchi Method for studying a large number of factors and interactions with only a few experiments is shortly presented and applied to the development of a tablet formulation.

INTRODUCTION

In this study it is attempted to develop a compressed tablet which has to meet different criteria such as : minimal friability, good porosity and as final goal maximal ability to bind macromolecules. To reach this goal, a designed multifactor experiment based on Taguchi's work has been used.

First, his basic philosophy is presented. Then, the methodology is applied to tablet development.

GENICHI TAGUCHI METHOD

Dr Genichi Taguchi, an engineer of quality assurance in a Japanese Company, developed a low cost method to rapidly improve a product's quality.

Taguchi believes that keeping the product's properties within specifications is only a beginning. When a target has been identified, one should try to hit the bullseye every time and not simply stay on the target. The cost of deviating from the bullseye increases quadratically [1]. Economic justification exists for this method since a perfect product avoids warranty costs, customer inconvenience or loss of goodwill for the company.

His goal has been to find a method to minimize variation in product and manufacturing process. The typical manufactors approach is to reduce variation and improve quality by removing the CAUSE of variation. Instead, Taguchi recommends to look at the process and product itself and reduce variation by removing the EFFECT of the cause [2]. This approach is attractive because in many production problems :

- one may never know the causes, or
- one may not be able to eliminate the causes even if it were known, or
- if one may eliminate it, it may be with a very high cost.

To realize such a study, there are two possibilities :

1) Changing only one factor each time according to Claude Bernard theories [3].

This linear, "one factor at a time approach", takes a long time.
Additionnaly it does not account for : – forgotten factors, or
– quantification of the factor's interaction

2) The second approach is to use an experiment design. Factorial experimentation consists of simultaneously change of many parameters according to a determinal design and also of analysing the obtained results with a variance analysis.

In all industrial processes, numerous parameters intervene. As the number of studied factors increases, it becomes more difficult to use such a plan (increase in the number of trials, mathematical complexity ...). This would not be simple, not to say that it is quite impossible, for a non–specialist [4].

Taguchi proposed a method which is easy to put into practice ; he proposed a limited number of orthogonal arrays taken from the 2^n design. These tables are presented in the form of matrices and are used in the construction of the experimental design.
Taguchi made the use of these tables extremely easy because of linear graphs. Certain graphs and interaction tables are associated to each design matrix.
An example of one of these is given in the experimental part of this paper.

Another great contribution of Taguchi Method is the Signal–To–Noise Ratio (S/N) [1,2,5]. It is well known that some factors have an effect on changing the mean, while others have an effect on changing the variability. The role of factors affecting variability is simply missed by conventional experimental methods. Taguchi called these extraneous variables "noise" and classified them into three types [2,6] :

- inner noise such as wear and tear, deterioration, clogging...
- outer noise, which includes incotrollable factors external to the process or product such as temperature, humidity, power supply, atmospheric pressure...
- between product noise, which corresponds to the small differences between products in the same batch.

A variance analysis realized on this ratio can demonstrate a significant effect of some factors formerly considered as insignificant.

Another interesting point is that this method is able to deal with a variety of data systems. Experimental results may, for example, be expressed by poor, acceptable or good [9].

The Taguchi Method, for identifying settings of design parameters that maximize a product quality, includes the following steps :

- Identify the target of the study.
- Identify the parameters with their settings or levels.
- Construct the design matrix and plan the parameter design experiment by using linear graphs.
- Conduct the parameter design experiment.
- Analyse and interpret results by using a variance analysis.

EXPERIMENTAL

1. Aim of the study

The tablet to be developped will be used in bio-technological fields. The target is to obtain a tablet with two criteria which determine the response variables :

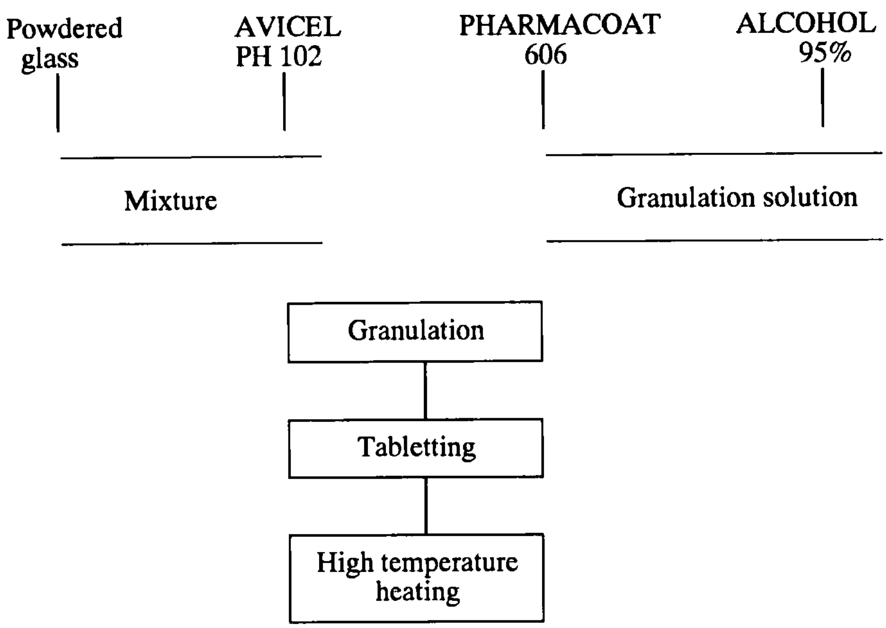
- a minimal friability,
- a high porosity.

2. Materials

The tablet formula contains :

- powdered glass with particles under 60 micrometers ;
- AVICEL PH 102 (microcrystalline cellulose) ;
- PHARMACOAT 606 (hydroxypropylcellulose) in 95% alcoholic solution.

TABLE 1
Steps of the manufacturing process



The process involves :

- mixture with a Turbula 2 A mixer,
- moist granulation on an oscillating granulator Erweka FGS mesh size 500 micrometers
- compression on a Korsch EKO machine equipped with strain gauges,
- high temperature heating.

Table 1 summarizes the different steps in the process.

3) <u>Identification of the parameters</u>

Identifying the parameters is one of the most important point in an experiment design. The choice of factors should result from a group discussion.

For this experiment six main (or controllable) factors were considered as interesting. One of the factors has four levels, five has two levels ; there are also two two-factors interactions gathered in table 2.

TABLE 2

Levels of factors studied in the experiment.

Letter	Factors	Level Low	Level High
A	Glass percentage (%)	40 50	60 70
B	PHARMACOAT percent in alcoholic solution (%)	7,5	10
C	Volume of the granulating solution (ml/30 g powder)	12	18
D	Punch adjustement	F1	F2
E	Heating temperature (degrees C)	680	780
F	Heating time (min.)	30	40

The tablet friability is measured by a rotating cylinder Erweka type TAP and the porosity by a mercury porosimeter.

4) Design matrix

As it has already been mentioned, Taguchi recommends the use of orthogonal arrays for planning parameter design experiments [7]. Constructing a design matrix requires the two following items :

- selection of the matrix type or table type depending on the number of factors studied and degrees of freedom,

TABLE 3

Degrees of freedom

Factors	Degree of freedom
A	3
B	1
C	1
D	1
E	1
F	1
A x C	3 x 1 = 3
D x C	1 x 1 = 1
Total	12

- selection of one of the linear graphs combined with the chosen table which will be usefull for matrix construction. This choice depends on the kind of problem studied and on the easiness of putting the experiment into practice.

4.1.) Table selection

Since there are six main factors and two interactions corresponding at twelve degrees of freedom (table 3), a $L_{16}\,(2)^{15}$ table has been selected (table 4).

The 16 in "L_{16}" indicates that the table includes sixteen lines or experiments and the $(2)^{15}$ that the table includes 15 columns for two-level factors. In fact because there is a four-level factor, the $L_{16}(2)^{15}$ is, in this study, transformed in a $L_{16}(2)^{12}(4)^{1}$. The vertical columns represent factors and interactions.

Figure 1 shows corresponding linear graphs.

Four different groups appear in table 4. The four groups enable to put the parameters into different categories of difficulties ; group one being the easiest and four the hardest (to put into practice).

TABLE 4

Table L_{16} [6]

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2
3	1	1	1	2	2	2	2	1	1	1	1	2	2	2	2
4	1	1	1	2	2	2	2	2	2	2	2	1	1	1	1
5	1	2	2	1	1	2	2	1	1	2	2	1	1	2	2
6	1	2	2	1	1	2	2	2	2	1	1	2	2	1	1
7	1	2	2	2	2	1	1	1	1	2	2	2	2	1	1
8	1	2	2	2	2	1	1	2	2	1	1	1	1	2	2
9	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
10	2	1	2	1	2	1	2	2	1	2	1	2	1	2	1
11	2	1	2	2	1	2	1	1	2	1	2	2	1	2	1
12	2	1	2	2	1	2	1	2	1	2	1	1	2	1	2
13	2	2	1	1	2	2	1	1	2	2	1	1	2	2	1
14	2	2	1	1	2	2	1	2	1	1	2	2	1	1	2
15	2	2	1	2	1	1	2	1	2	2	1	2	1	1	2
16	2	2	1	2	1	1	2	2	1	1	2	1	2	2	1
Group	1	2		3				4							

In practice changing the level of a factor is easier for some parameters (heating time for example) than for others (heating temperature or punch adjustment...).

Taguchi's table groupe 1 will always be reserved for the most difficult process variable because the level will change only one time.

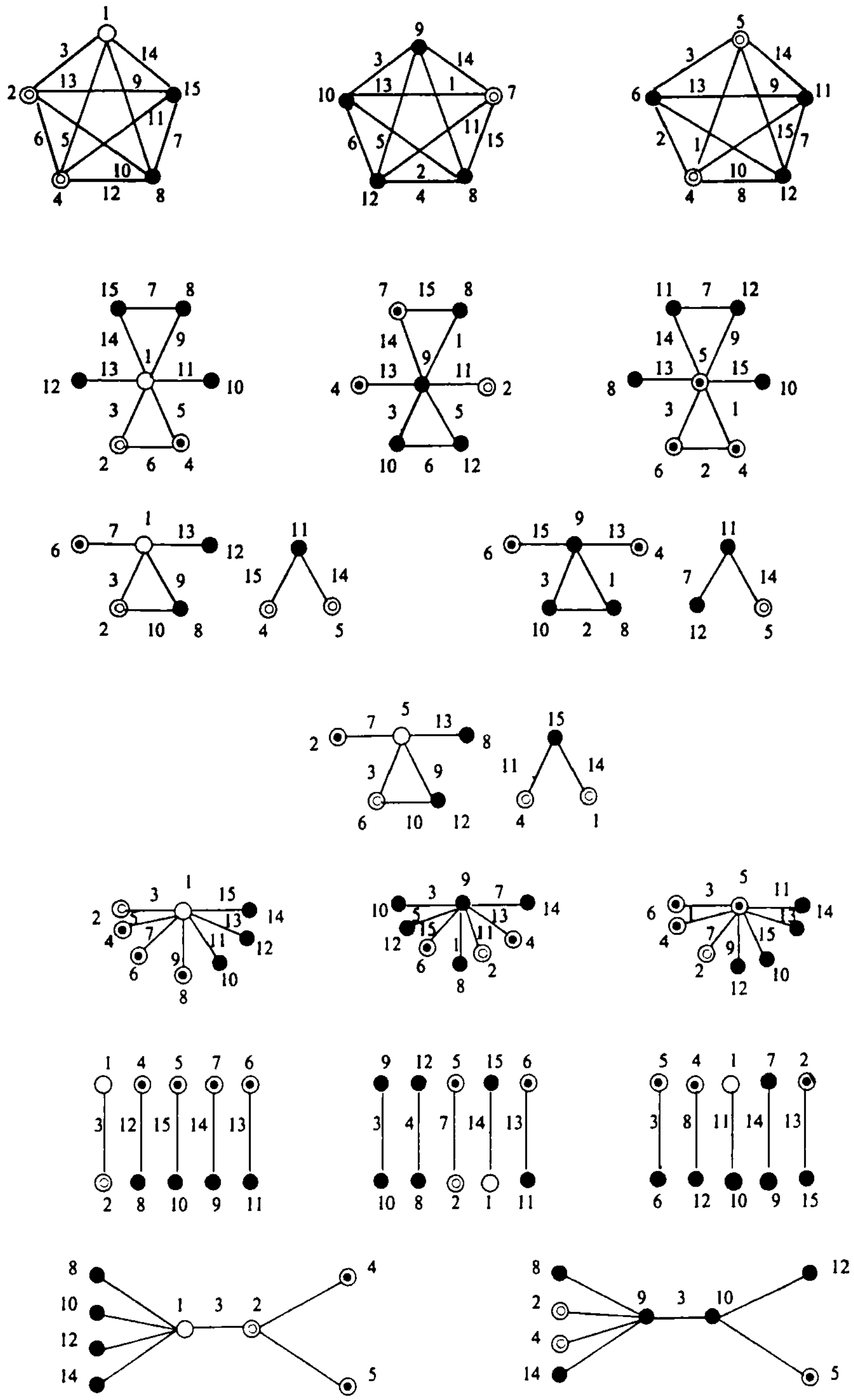


FIGURE 1

Examples of linear graphs according with a L_{16} table [6]

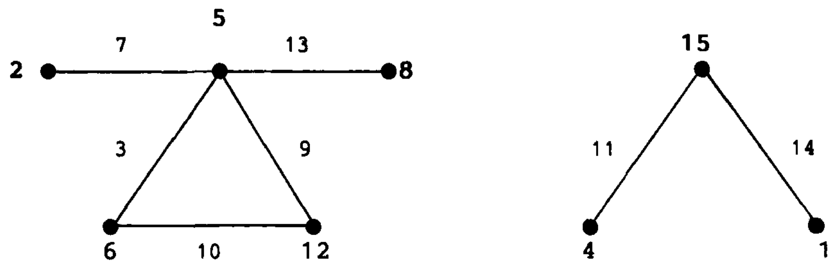


FIGURE 2

Linear graph used to construct the matrix

4.2.) Linear graphs selection

The restraints of the design must not be forgotten. The aim is to obtain information about :

- factor A with four levels ; this use three related columns to create a new column including the four levels because in a table L_{16} each column is proposed for only two-level factors ;
- factors B, C, D, E and F ;
- interactions AC (needs three columns) and DC.

Factor E (oven temperature) is the most difficult to adjust, therefore it will be in column 1.

The graph represented on figure 2 allows to construct the matrix.

4.3.) Creation of a four-level column

To create the new column for factor A, two columns and their interaction have to be taken. One solution is :

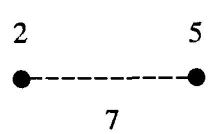


TABLE 5 a

Creation of a four level column

	Factors Column					
Experiment	1	2	3	4	5	Factor A
1		1			1	1
2		1			1	1
3		1			2	2
4		1			2	2
5		2			1	3
6		2			1	3
7		2			2	4
8		2			2	4
9		1			2	2
10		1			2	2
11		1			1	1
12		1			1	1
13		2			2	4
14		2			2	4
15		2			1	3
16		2			1	3

TABLE 5b

Creation of a four level column

	Column 5	
Column 2	1	2
1	1	2
2	3	4

Columns 2, 5, 7 will be replaced by the new one (table 5a). Columns 2 and 5 are taken and matched up with level 1, 2, 3 or 4 from table 5b.

For example experience 6 shows (table 5a) level 2 in column 2 and level 1 in column 5 corresponding to level 3 on table 5b ; this allows factor A to be matched up with level 3 in the experiment 6.

4.4.) Column assignment

Factor A (glass percent) : new column creation and removal of columns 2,5 and 7.

Factor C (granulating solution volume) : can be assigned to column 6 or 12 since the purpose is to study the AC interaction.

Factor D (punch adjustement) : will be assigned to the third top of the triangle since DC interaction must also be studied. Since it is more difficult to fix D than C, D is assigned to column 6 which belongs to groupe 2, and C to column 12 (group 3).

Factor E (oven temperature) : column 1 (see above).

Interaction AC : The interaction AC is represented by :

- column 9 which corresponds to the interaction between column 5 (factor A) and column 12 (factor C) (see figures 2 and 3) ;
- column 11 : interaction between columns 7 and 12
- column 14 : interaction between columns 2 and 12

In fact it is necessary to take into account interactions between 12 (factor C) and 2, and interactions between 12 and 7 since these two columns (2 and 7) have been used to create the factor A column.

11 and 14 are obtained from the interactions table (table 6).

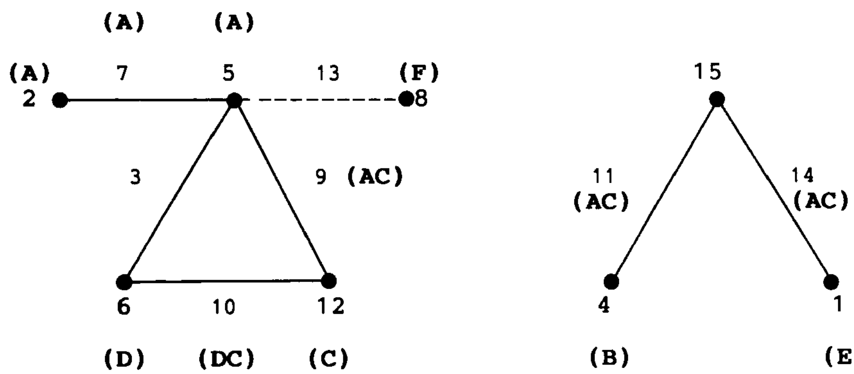


FIGURE 3

Linear graph and column assignment used in the experiment design

TABLE 6

Interactions table [6]

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
(1)	3	2	5	4	7	6	9	8	11	10	13	12	15	14
	(2)	1	6	7	4	5	10	11	8	9	14	15	12	13
		(3)	7	6	5	4	11	10	9	8	15	14	13	12
			(4)	1	2	3	12	13	14	15	8	9	10	11
				(5)	3	2	13	12	15	14	9	8	11	10
					(6)	1	14	15	12	13	10	11	8	9
						(7)	15	14	13	12	11	10	9	8
							(8)	1	2	3	4	5	6	7
								(9)	3	2	5	4	7	6
									(10)	1	6	7	4	5
										(11)	7	6	5	4
											(12)	1	2	3
												(13)	3	2
													(14)	1

TABLE 7

Table L16 used in the experiment design

									A	D	A			A		
	E			B		D		F	C	C	C	C		C		A
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	A
1	1		1	1		1		1	1	1	1	1	1	1	1	1
2	1		1	1		1		2	2	2	2	2	2	2	2	1
3	1	U	1	2	U	2	U	1	1	1	1	2	2	2	2	2
4	1	s	1	2	s	2	s	2	2	2	2	1	1	1	1	2
5	1	e	2	1	e	2	e	1	1	2	2	1	1	2	2	3
6	1	d	2	1	d	2	d	2	2	1	1	2	2	1	1	3
7	1		2	2		1		1	1	2	2	2	2	1	1	4
8	1		2	2		1		2	2	1	1	1	1	2	2	4
9	2	f	2	1	f	1	f	1	2	1	2	1	2	1	2	2
10	2	o	2	1	o	1	o	2	1	2	1	2	1	2	1	2
11	2	r	2	2	r	2	r	1	2	1	2	2	1	2	1	1
12	2		2	2		2		2	1	2	1	1	2	1	2	1
13	2		1	1		2		1	2	2	1	1	2	2	1	4
14	2	A	1	1	A	2	A	2	1	1	2	2	1	1	2	4
15	2		1	2		1		1	2	2	1	2	1	1	2	3
16	2		1	2		1		2	1	1	2	1	2	2	1	3
Group	1	2			3						4					

Interaction DC is represented by column 10 (see linear graph figures 2 and 3).

Now columns 4, 15 and 8 are left for main factors, columns 3 and 13 are left for interactions, and factors B (Pharmacoat percent) and F (heating time) have still to be placed.

The levels of both of these factors are easy to change, so it is possible to arbitrarily assign **factor B** to column 4 and **factor F** to column 8.

TABLE 8

Levels used for test 7

Factor	Level	Value
A	4	70%
B	2	10%
C	2	18 ml
D	1	F1
E	1	680°C
F	1	30 min

Now all factors are assigned ; a linear graph and corresponding L_{16} table (figure 3 and table 7) result from this assignment.

Columns 3, 13 and 15 are free and available to calculate the residual. In such a graph (figure 3), it is necessary to point out that column 13 cannot be considered as the whole interaction between columns 5 and 8 because 5 representes only a part of factor A.

EXPERIMENTS

The experiments are performed by assigning them to the levels indicated in the table 7 for each test. For example test 7 corresponds to (table 8) .

RESULTS AND INTERPRETATION

Graphical analysis, variance analysis of the mean and of the Signal–to–Noise ratio allow to :

– detect factors and interactions affecting the quality of the tablets : A, C, D and E ;

- determine the optimal level of studied factors :
  A_2 (glass percentage) = 50 %
  C_2 (volume of granulating solution) = 18 ml/30 g
  D_1 (punch adjustment) = F1 (low value)
  E_1 (heating temperature) = 780°C

CONCLUSIONS

The Taguchi Method is based on removing the effect of the cause of variation. This japanese engineer recommended the use of orthogonal arrays and proposed linear graphs to construct easily a design matrix.

This method allows to study a large number of factors and interactions with only a few experiments and take into account factors affecting variability.

REFERENCES

1) L. Ealey – Taguchi methods the thought behind the system – Automotive industries, feb., 68 – 70 (1988).

2) R. Copp – Report on japanese quality engineering using designed experiments : The Taguchi method – American Supplier Institute – MI 48174 Romulus USA.

3) C. Haberer – Plans d'expériences – Personnal communication.

4) J. Fleury – Introduction à l'usage des méthodes statistiques en pharmacie – Médecine et Hygiène Ed., Genève, 1987.

5) J.S. Hunter – Statistical Design Applied to Product Design – J. Quality Technology, **17**, 4, 210 – 221 (1985).

6) M. Vigier – Pratique des plans d'expérience : Méthodologie Taguchi – Les Editions d'Organisation Ed., Paris, 1988.

7) R.N. Kackar – Off–line quality control, parameter design and the Taguchi method – J. Quality Technology, **17** , 4, 176 – 188 (1985).