INVESTIGATION INTO THE EFFECTS OF SOME BINDERS ON TABLET PROPERTIES USING TREND ANALYSIS

E. O. Akala, F. O. Adewole, O. O. Komolafe and T. O. Ogundipe

Department of Pharmaceutics
Faculty of Pharmacy
University of Ife,
(Now Obafemi Awolowo University)
Ile-Ife, Nigeria.

ABSTRACT

Modern techniques in drug product design and process development demand the establishment of the relationship between independent variables (formulation and process variables) and the response variables (tablet properties) by means of a mathematical equation. Such equations are often valuable when various factors are to be combined to optimize a particular drug product property.

A technique for describing the response to varying levels of a quantitative factor is trend analysis (determination of regression model through the use of orthogonal polynomials). The technique is equivalent to using the method of least squares, but it has the advantage that while tests are carried out to determine whether or not statistically significant differences exist among the various factors and levels of factor(s) of interest, information about the functional relationship between treatments and response can be found. Moreover, the use of orthogonal polynomials permits the test of each regression coefficient in the polynomial equation independently of the others and thus helps to select the terms that should be included in the regression model.

A requirement in the design of an experiment to make it amenable to trend analysis is that the levels of a given factor should have equal intervals. Consequently we used commonly available binding agents to design experiments to satisfy this requirement and to demonstrate the technique. The experiments were designed to compare the effects of various concentrations of acacia, cassava starch and gelatin binders on tablet properties using analysis of variance and orthogonal polynomials to obtain equations which estimate the response (tablet property).

Using lactose as the base material, five levels of each binder were used in the preparation of tablets. With such five treatments, the highest degree of polynomial that can be tested is fourth. Results show that a first-degree, second-degree and third-degree polynomials respectively best describe the effect of cassava starch, gelatin and acacia binders on tablet hardness while a first-degree polynomial best describes the effect of the binders on disintegration time.

INTRODUCTION

The design of any drug delivery system involves a number of variables:

a) Formulation and process variables (independent variables) These variables are controllable (i.e. the level of a given ingredient or the mixing time for a given process step).

b) The properties or characteristics of the resultant drug delivery system constitute the second group of variables (dependent variables). The pursuit of the relationshp between the two groups of variables has been the main concern of pharmaceutics.

Though a lot of work had been done to investigate these variables, the functional or mathematical relationship between the formulation and/or process variables and the response varibales was not often considered. For example, some workers evaluated some substances as binders in sulfathiazole tablets and ranked them in order of hardness imparted to tablets as well as to classify them functionally as exhibiting sugar-like or gum-like behaviour (1). Literature is replete with such qualitative description of experimental data. Experimental results presented in that way do not offer much information for use in drug product development, as new techniques in drug product design and process development demand the establishment of the relationship between response variables and the independent factors by means of a mathematical equation. Such equations are often valuable when various variables are to be combined to optimize a particular drug product property (i.e. to manufacture a new product with certain desired characteristics or to obtain an old product more economically).

Most of the methods of carring out optimization assume that a mathematical relationship exists which relates the response variables to levels of controllable variables. However, the formulation or drug product development pharmacist does not know **a priori** the theoretical equation for the drug product of interest because the underlying mechanisms in pharmaceutical product and process design problems are complicated and there is no knowledge of the natural laws governing the system(2). Thus the formulator has to generate the relationships between the variables of his particular formulation from experimental data. The resulting equation is the basis of optimization. Regression analysis based on the method of least squares is the most common procedure for determining

mathematical relationship between dependent and independent variables. Another technique is trend analysis (determination of regression models through the use of orthogonal polynomials).

The work reported here was undertaken to demonstrate the use of trend analysis in obtaining polynomial models relating response variables (tablet crushing strength and disintegration time) to the independent variable (binder concentration). The technique involves performing a set of statistically designed experiments (i.e. evenly spaced binder concentration replicated twice) and using the resulting data to derive a mathematical model. An equation is generated for each dependent variable which relates it to the levels of the independent variable.

Materials and Methods

Lactose BP (Whey Products, U. K.) was sifted through mesh 60. Magnesium stearate B. P. was from Hopkins and Williams, Essex. Cassava starch was prepared in the laboratory from the tubers of **Mannihot utilissima.** Gelatin was from Hopkin and Williams, Essex. Acacia B. P (Powdered Gum Acacia) was from Courtin and Warner, Lewes-Sussex.

Five hundred grammes (500g) of lactose powder was put in a Z-blade mixer (Erweka Apparatebau, F. R. Germany) and dry blended for two minutes. Predetermined quantities of freshly prepared binder mucilage or solution (Table 1) were added to the lactose powder in 4 portions and mixing was carried out for 2 minutes after each addition. When the whole quantity of the binder was added, mixing was continued for two more minutes. The moistened mass was forced through a 1.40 mm screen using a Jackson and CrocKatt Granulator, dried in a fluidized bed drier (Glatt Apparatebau, F. R. Germany), with an inlet air temperature of 45-50°C to a residual moisture content of approximately 1%. The dried granules were rescreened through a 1.40 mm screen.

Compression of Tablets: Each batch of granules was intimately mixed with o.5% w/w of magnesium stearate and then compressed to tablets using 12mm flat punches on a single-punch machine (Diaf A/S, Denmark). The first 20 tablets and the last 20 - 50 tablets were rejected to eliminate weight variation due to initial flow resistance, insufficient weight of granules and excess fines (3). All the adjustments of the machine were kept constant.

Tablet characteristics: Mean crushing strength of 10 tablets was determined using a Pfizer Hardness Tester. B. P. method was used for measuring disintegration time with the Manesty Table Disintegration Test Unit using distilled water as the medium at 37 ± 1°C.

Results and Discussion:

Since we have more than two levels of binder concentration, multiple comparison procedure (Analysis of variance) together with F - test of significance was adopted. Partioning of the Total Variability in the Experimental Results:

The observed differences in terms of tablet crushing strength and disintegration time among the various batches for each type of binder consist of:

(i) A component due to differential treatment effects (i.e. Graded changes in binder concentration).
(ii) A component due to replication
(iii) A component resulting from natural variation (Experimental error)

The sum of squares for each source of variation was calculated using standard formulas (4,5). The variances of the sources of variation were then computed from the sum of squares and the degrees of freedom. The results are shown in tables 2a - 7a. The results indicate that the treatment effect (i.e. graded changes in binder concentration) produced statistically significant differences in the mean values of the tablet crushing strength and disintegration time. However, the results do not indicate which batch has the highest or lowest value for the tablet crushing strength or the longest or shortest disintegration time.

Statistical techniques abound in the literature for answering the question. One of them (relevant to this work) is trend analysis which is discussed below.

Partitioning of Treatment Sum of Squares Using Orthogonal Polynomials:

Having compared the treatments (various batches of the tablets) and found that significant differences exist among them, the interest now is to assess how changes in the dependent variable (binder concentration) effect the response variables. With five treatments (binder concentrations) the highest degree of polynomials permits the test of regression coefficients (b's in the polynomial equation:

$Y = b_c + b_1 X + b_2 X^2 + ... b_p X^2) .....$ Equation 1) in dependently of others. Thus the treatment effect, which was found significant (Tables 2a - 7a) is partitioned into several components belonging to linear, quadratic, cubic and quartic. Each component is then tested against the experimental error mean square. The result indicates the type of polynomial that best describes the response function.

The steps are summarized below; the details can be checked in the literature (6).

(a) Obtain tables of orthogonal polynomial coefficients and the sum of squares of the coefficients. The tables of values of the orthogonal polynomial coefficients make the work of calculating the linear, quadratic, cubic etc. components a simple matter.

(b) Multiply the appropriate orthogonal polynomial coefficients by the treatment totals (i.e. the sum of values of the response variable for each level of a given independent variable).

(c) Divide the result by the product of the sum of squares of the coefficient and the number of replicate. The result gives the sum of squares.

(d) The F - ratios are obtained by dividing the sum of squares of each component by the experimental error

mean square.

The results obtained are shown in tables 2b - 7b.

The Crushing Strength:

Acacia Gum Binder: The results shown in table 2b indicate that linear, quadratic and cubic effects are significant. Both linear and quadratic effects are highly significant. Thus on the average, the tablet crusing strength increases as binder concentration. The cubic component shows that there is one peak (maximum) and one depression (minimum) in the curve of tablet crushing strength versus binder concentration (i.e. non-uniform increase in tablet crushing strength as binder concentration increases). The results suggest fitting a polynomial model of the third order (i.e. a cubic equation) through the means of tablet crushing strength. (6)

The equation obtained is shown below:

$Y = 1.498x^3 — 8.964x^2 + 17.964x — 2.822$ ..... Equation 2 where Y is the estimated tablet crushing strength (K_s) and X is the binder concentration (% w/w). The equation was used to draw the line of best fit through the means of the values of tablet crushing strength (Fig 1.)

Cassava Starch Binder:- The analysis, as shown in table 3.b, indicates that only the linear effect is significant and it is highly significant. It is a linear response indicating that on the average tablet crushing strength increases proportionately with increment in binder concentration. A linear equation that best fits the data was obtained using the technique of orthogonal polynomials (6). The equation is shown below:

$Y = 3.136 + 3.227x$ ..... Equation 3. The line of best fit through the means of tablet crushing strength was obtained with the aid of equation 3 (Fig. 1). Gelatin Binder:- As shown in table 4b, the linear and the quadratic effects are significant. The linear effect is highly significant. The indication is that on the average, the tablet crushing strength increases as the binder concentration. The linear component is the portion of the sum of squares attributable to the linear regression of tablet crushing strength on binder concentration. The quadratic component measures additional improvement due to fitting the second-degree polynomials. It shows that the increase in hardness becomes suggests fitting a second-degree polynomial curve through the means of tablet crushing strength. The equation obtained is:

$Y = 4.813 + 3.632X — 0.673X^2$ ..... Equation 4.

The increase in tablet crushing strength with increase in binder concentration is a reflection of the increasing binding capacity of the binders at high concentrations, leading to a greater bondinjg force among granules during compression (7, 8, 9).

Disintegration Time:

Tables 5b — 7b show that only the linear effect is significant and that it is highly significant. Thus for all the three binders investigated, disintegration time increases proportionately with increment in binder concentration. Equation 5, 6 and 7 respectively relate the disintegration times of the tablets to levels of Gum Acacia, Cassava starch and Gelatin binders:

$Y = 13.280 + 2.318X$..... Equation 5

$Y = 10.134 + 9.676X$ .....Equation 6

$Y = 11.150 + 6.563X$ ..... Equation 7

The equations were used to fit lines of best fit through the mean disintegration time (fig 2).

The increase in disintegration time with increase in binder concentration is attributed to the formation of a thin film of the binders around the granules; the thickness of the film is dependent on the quantity (concentration) of the binder employed. (7. 8, 9, 10).

The sum of residuals was calculated for each equation and found to be zero showing the validity of the equations.

Conclusion:

The use of trend analysis in the establishment of the founctional relationship between an independent variable (binder concentration) and response variables (tablet crushing strength and disintegration time) has been demonstrated with a very simple system - one evenly spaced quantitative factor. Trend analysis finds its greatest use in multifactor esperimental design like those commonly encountered in dosage form design. In such factorial experiments, interdependence of factors of production is comon. Trend analysis allows the determination of the proper regression and also indcates the present or absence of interation among the independent variales. Such information can aid the researcher in deciding not only on the particular interaction among the independent variables. Such information can aid the researcher in deciding not only on the particular interaction terms that should be included in the regression models but also on the specific form that each interaction term should take.

References

1. E. Nelson, J. R. ARNDT, L. W. BUSSE. J. Am. Pharm. Ass. Sci. Ed., 46 (4) 1957).
2. D. E. FONNER, Jr., J. R. BUCK and G S. Banker, J. Pharm. Sci., 59; 1587 (1970).
3. A. M. MARKS, J. J. Sciarra. u. Pharm. Sci. 57, 497 (1968).
4. R. L. ANDERSON, T. A. BANCROFT. "Statistical Theory in Research" McGraw-Hill, New York, 1952 P. 210.
5. B. Ostle, "Statistics in Research" 3rd Ed. Towa State University Press, Iowa, 1963. P. 194
6. R. H. MYERS, Response Surface Methodology" Allyn and Bacon, Boston, Mass, 1971 P. 35.
7. S. ESEZOBO, V. AMBUJAM.: J. Pharm. Pharmacol. 34, 761 (1982).
8. W. L. DAVIS, W. T. GLOOR. Jr.: J. Pharm. Sci. 61, 618 (1972)..
9. R. N. NASIPURI, E. O. AKALA,: The Nig. J. Pharm. 17: 13 (1986).
10. A. A. CHALMERS, P. H. ELWORTHY.: J. Pharm. Pharmacol. 28(3); 233 (1976).

COMPOSITION OF LACTOSE GRANULES

Table 1:

Binder Type	Acacia Gum					Cassava starch					Gelatin				
Mucilage or Solution concentration % w/w	4	8	12	16	20	4	8	12	16	20	4	8	12	16	20
Concentration of the binder % w/w in Dry Granules	0.56	1.12	1.68	2.24	2.80	0.6	1.2	1.8	2.4	3.0	0.48	0.96	1.44	1.92	2.40
Lactose (g)	500 (70g of the mucilage was used).	500	500	500	500	500 (75g of the mucilage was used)	500	500	500	500	500 (65g of the solution was used.	500	500	500	500

Table 2a. Analysis of Variance on the Effects of Acacia Gum Binder on Tablet Crushing strength (kg).

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	Observed F.	Tabulated F 5%	Tabulated F 1%
Replicate	1	0.40000	0.40000	2.02737	7.71	21.20
Binder Concentration	4	19.98056	4.99514	** 25.17486	6.39	16.00
Experimental Error	4	0.78920	0.19730			
Total	9	21.16976				

* Significant

** Highly significant

Table 2.b.: Analysis of variance for the Polymomial Models for the Effect of Treatment (Acacia Gum Binder concentration) on Tablet Crushing strength.

Effect	Degree of Freedom	Sum of Squares	Observed F
Linear	1	12.48200	** 63.26
Quadratic	1	5.49143	** 27.83
Cubic	1	1.98450	* 10.06
Quantic	1	0.02263	0.115

* Significant

** Highly significant

Table 3a. Analysis of Variance on the Effects of Cassava Starch Binder on Tablet Crushing strength (Kg)

Source of Variation	Degrees of Freedom	Sum of Square	Mean Square	Observed F	Tabulated F 5%	Tabulated F 1%
Replicate	1	0.00500	0.00500	0.05549	* 7.71	21.2
Binder Concention	4	75.12464	18.78116	** 208.44800	6.39	16.00
Experimental Error	4	0.36040	0.09010			
Total	9	75.49004				

Table 3b:- Analysis of Variance for the Polynomial Models for the Effect of Treatment (Cassava Starch Binder Concentration) on Tablet Crushing Strength.

Effect	Degree of Freedom	Sum of Squares	Observed F
Linear	1	74.96192	** 831.99
Quadratic	1	0.09143	1.02
Cubic	1	0.06498	0.72
Quartic	1	0.00631	0.07

Table 4a: Analysis of Variance on the Effectsoof Gelatin on Tablet Crushing Strength (Kg).

Source of Variation	Degrees of Freedom	Sum of Square	Mean Square	Observed F	Tabulated F 5%	Tabulated F 1%
Replicate	1	0.00361	0.00361	0.04990	7.71	21.20
Binder Concentration	4	14.34034	3.58509	** 49.55889	6.39	16.00
Experimental Error	4	0.28934	0.07234			
Total	9	14.63329				

Table 4b:- Analysis of Variance for the Polynomial Models for the Effect of Treatment (Gelatin Binder Concentration) on Tablet Crushing Strength:

Effect	Degree of Freedom	Sum of Squares	Observed F
Linear	1	13.23565	** 102.98
Quadratic	1	0.67580	* 9.34
Cubic	1	0.01740	0.24
Quartic	1	0.41149	5.69

Table 5a.: Analysis of Variance on the Effects of Acacia gum binder on Tablet Disintegration Time (Mins.)

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	Observed	Tabulated F 5%	Tabulated F 1%
Replicate	1	0.04624	0.04624	0.04859	7.71	21.2
Binder Concentration	4	35.91474	8.97869	* 9.43417	6.39	16.00
Experimental Error	4	3.80686	0.95172			
Total	9	39.76784				

Table 5b:- Analysis of Variance for the Polynomial Models for the Effect of Treatment (Acacia Binder Concentration) on Disintegration Time:

Effect	Degree of Freedom	Sum of Squares	Observed F
Linear	1	33.74802	** 35.46
Quadratic	1	0.28000	0.29
Cubic	1	1.35720	1.43
Quantic	1	0.52952	0.56

Table 6a:- Analysis of Variance on the Effects of Cassava starch Binder on Tablet Disintegration Time (Mins).

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	Observed F	Tabulated F 5%	Tabulated F 1%
Replicate	1	0.28561	0.28561	0.19126	7.71	21.2
Binder Concentration	4	677.0.2246	169.25562	** 113.34031	6.39	16.00
Experimental Error	4	5.97334	1.49334			
Total	9	683.28141				

Table 6b:- Analysis of Variance for the Polynomial Models for the Effect of Treatment (Cassava Starch Binder Concentration) on Disintegration Time.

Effect	Degree of Freedom	Mean Square	Observed F
Linear	1	673.84441	** 451.23
Quadratic	1	0.52389	0.35
Cubic	1	2.57762	1.73
Quartic	1	0.07654	0.05

Table 7a:- Analysis of Variance on the Effects of Gelatin Binder on Tablet Disintegration Time (Mins.)

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	Observed F	Tabulated F 5%	Tabulated F 1%
Replicate	1	1.60000	1.60000	4.57143	7.71	21.20
Binder Concentration	4	199.40000	49.85000	** 142.42857	6.39	16.00
Experimental Error	4	1.40000	0.35000			
Total	9	202.40000				

Table 7b:- **Analysis of Variance for the Polynomial Models for the Effect of Treatment (Gelatin Binder Concentration) on Disintegration Time.**

Effect	Degree of Freedom	Sum of Square	Observed F
Linear	1	198.45000	567.00**
Quadratic	1	0.89286	2.55
Cubic	1	0.05000	0.143
Quartic	1	0.00714	0.02

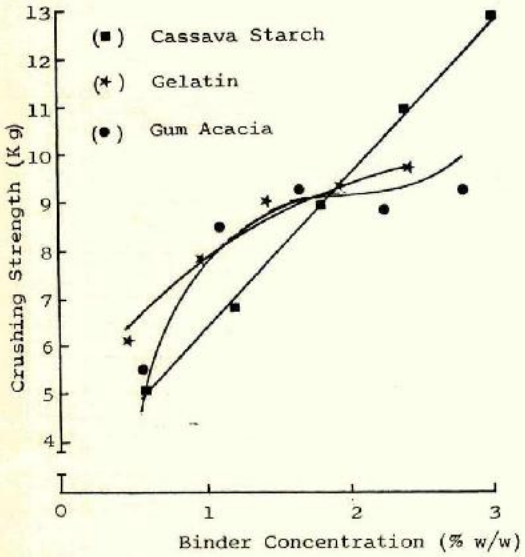

Fig 1: Effect of Binder Concentration on Tablet Crushing Strength (Kg)

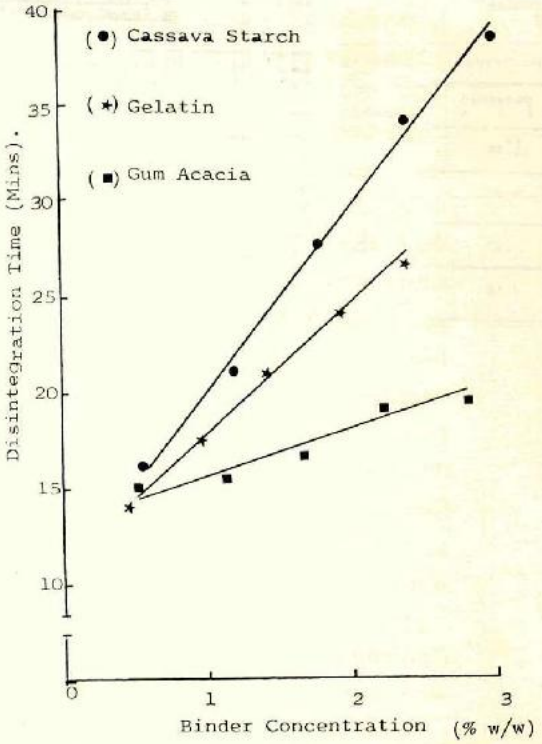

Fig 2: Effect of Binder Contration on Disintegration Time.