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An evaluation of the relative importance of formulation and process variables using factorial design

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A factorial design method for assessing the relative importance of various formulation and process factors and their interactions in model paracetamol tablets is described. The design was a 2 × 2 × 2 × 3 type using mixing time, starch concentration, drug particle size and compaction pressure respectively. The starch concentration was the most significant factor in affecting the dissolution rate but the larger drug particle size also gave a significant increase in drug release rate. Interactions between starch concentration and drug size and between these and mixing time were also observed. The most significant factor affecting the tensile fracture stress of the tablets was the mixing time, followed in order by the drug particle size, starch concentration and compaction pressure.

The formulation of a disintegrating tablet is a complex process dependent on many interacting variables. Those affecting in-vitro drug dissolution include the characteristics of the drug itself, particularly its surface area or particle size (Tuladhar et al 1983), the disintegrant type and concentration (Rudnic et al 1981; Smallenbroek et al 1981), and the presence of other excipients, especially lubricants (Jaiyeoba & Oladiran 1983).

The effects of the ingredients in a formulation may be modified by the process used to combine them. For example, studies on different methods of granulation such as wet granulation, spray drying, roller compaction and direct compression have been shown by Seager et al (1981) to be related to binder distribution in a tablet. Even when the granulation method and formulation are fixed, it is still possible to alter the tablet characteristics by altering the method used to add the dry excipients. This has been shown by Bolhuis et al (1975) with respect to lubricant mixing in a direct compression formulation.

In addition to the effects of powder and granule modifications, the effect of the compaction process cannot be neglected. The compaction pressure and the timing of the compression/ejection cycle may exert an appreciable influence on the tablet characteristics. Differences in the compression cycle on different machines are often the cause of scale-up problems and this has led to the development of tablet machine simulators (Hunter et al 1976). The effect of compaction pressure on dissolution has been studied (Finholt 1974; Miller et al 1980) and might best be described as being dependent on the characteristics of the drug involved, mainly its fragmentation propensity, as well as the characteristics of the tablet matrix.

These and many other studies have contributed considerably to an understanding of the basic mechanisms involved in tablet formulation, but the relative importance of the individual interactions to the final tablet characteristics remains comparatively neglected.

The technique of factorial design is an efficient method of indicating the relative significance of a number of variables, and their interactions, in the production of a given result. This technique is well documented in a variety of fields, but has only been applied infrequently to pharmaceutical formulation (Newton & Razzo 1977; Malinowski & Smith 1975; Adeyemi & Pilpel 1983).

In this study the effects of two processing factors, mixing time and compaction pressure, and two formulation factors, starch concentration and drug particle size, on the dissolution rate and tablet strength are examined in a model direct compression system.

MATERIALS AND METHODS

Materials

An Alpine zig-zag classifier was used to separate paracetamol BP into two size fractions, above and below a nominal cut size of 20 μm. Aerosil 200 and magnesium stearate were screened through 125 μm sieves before use. The mean surface volume diameter of all the ingredients except the Aerosil 200

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was determined on a Fisher sub-sieve sizer at a porosity of 0·6. The sizes are shown in Table 1.

Table 1. Particle size of ingredients.

Material	Mean surface-volume diameter (μm)
Paracetamol BP +20	20·4
Paracetamol BP −20	7·3
Avicel PH101	8·2
Maize starch	14·0
Magnesium stearate	2·5

Methods

Twenty-four trials were required for the complete experimental design, with three factors examined at two different levels and one factor at three different levels (Table 2). The mean fracture stress and mean time for 90% dissolution for each trial were used as the experimental determinants, and by combining the determinants of the 24 trials, the effect of one factor, or the interaction of factors on the determinant were assessed. The formulations and batch size are shown in Table 3.

The powders were mixed for 1 or 5 min in a modified Hobart high shear mixer at 1750 rev min^{-1}. Each powder mixture was assayed for drug content by the BP (1980) method for paracetamol tablets.

Table 2. Experimental variables used in each trial.

Trial number	Mixing time (min)	Starch concn (%)	Drug size (μm)	Compaction pressure (MNm−2)
1	1	1	+20	100
2	1	1	+20	150
3	1	1	+20	200
4	5	1	+20	100
5	5	1	+20	150
6	5	1	+20	200
7	1	7	+20	100
8	1	7	+20	150
9	1	7	+20	200
10	5	7	+20	100
11	5	7	+20	150
12	5	7	+20	200
13	1	1	−20	100
14	1	1	−20	150
15	1	1	−20	200
16	5	1	−20	100
17	5	1	−20	150
18	5	1	−20	200
19	1	7	−20	100
20	1	7	−20	150
21	1	7	−20	200
22	5	7	−20	100
23	5	7	−20	150
24	5	7	−20	200

Table 3. Experimental formulations with 1% and 7% starch.

Paracetamol	25·0	25·0
Avicel	72·9	66·9
Maize Starch	1·0	7·0
Aerosil	0·1	0·1
Magnesium stearate	1·0	1·0
	100·0%	100·0%
Batch size 500 g		

The tablets were compressed at 3 pressures on an instrumented Manesty F3 machine using 12·5 mm flat-faced punches, to produce tablets containing 100 mg drug (approximately 400 mg tablet weight). Instrumentation consisted of balanced strain gauge load cells at the base of the upper and lower punch holders, connected via a Wheatstone bridge circuit to a Fylde 154ABS amplifer and a Bryans Southern 40 000 ultraviolet galvanometer. Tablets were weighed (±0·0001 g) and their thickness measured (±0·01 mm) by micrometer screw gauge after storage at 25 °C/33% RH for at least 24 h.

Six tablets selected at random from a trial were subjected to a modified USP paddle method dissolution test. The dissolution medium was 900 ml 0·1 M HCl at 37 °C stirred at 100 rev min^{-1} in an Erweka DT D6 dissolution apparatus. The absorbance of the solution was measured at 270 nm at 1 min intervals using a continuous flow system consisting of a Watson Marlow 501S50 pump and a Kontron Uvikon 810 spectrophotometer linked to a Commodore Pet 8032 computer for data capture.

The mean dissolution profile of the six tablets was used to determine the time for 90% of the drug to dissolve, the level part of the profile being taken as 100%. The times for 50 and 60% dissolution were also determined.

Tablet tensile fracture stress was calculated for ten tablets from each trial using a diametral compression test (Fell & Newton 1970) and the breaking load determined on an Engineering Systems (Nottingham) Ltd CT40 tablet strength tester.

RESULTS AND DISCUSSION

Mean times for 90% dissolution (T90%) and tensile fracture stress for each trial are shown in Table 4. These were analysed independently by a computer method (Genstat 1980) to show the analysis of variance (ANOVA) relating to different factors and interactions (Tables 5 and 6). A discussion and explanation of the statistics involved may be found in Davies (1967). The process consists essentially of the

analysis of variance of the mean effects from the whole experimental design which can be associated with one or more of the experimental factors. The significance is then calculated from an 'F' test on the variance ratio. The subsidiary Tables (5a–d, 6a–d) show the mean effects attributable to the significant factors and interactions.

Table 4. Mean values for each trial.

Trial number	Tensile fracture stress (MNm^{-2})	T90% (min)
1	0·909	30·84
2	1·051	34·47
3	1·106	30·19
4	0·383	25·56
5	0·541	18·39
6	0·571	13·11
7	0·689	3·95
8	0·825	4·12
9	0·871	4·77
10	0·287	10·52
11	0·410	9·46
12	0·443	10·21
13	1·185	31·67
14	1·473	45·87
15	1·551	57·30
16	0·732	43·99
17	0·831	60·21
18	1·007	54·44
19	0·972	14·06
20	1·182	14·02
21	1·378	13·66
22	0·362	4·77
23	0·678	5·63
24	0·743	8·53

The ANOVA Table using tensile fracture stress as the experimental determinant (Table 5) shows that the most significant factor is the mixing time. The reduction in mean tensile fracture stress attributable to the increase in mixing time (Table 5a) is probably due to the formation of a layer of magnesium stearate around the particles causing a reduction in interparticulate bond strength as elucidated by Bolhuis et al (1975). Of slightly lower significance, although still above 99%, are the effects of drug particle size on tensile fracture stress. The mean tensile fracture stress attributable to drug particle size is shown in Table 5c. This shows that the reduction in tensile fracture stress on increasing the drug particle size is less than that of increasing the mixing time. The effect of drug particle size may be due to the higher specific surface of the smaller size fraction resulting in an increased surface area available for bonding on compaction, with a concomitant reduction in the inter-bond concentration of magnesium stearate. It is also possible that some of the energy transmitted to the system on compaction is

Table 5. ANOVA table based on fracture stress.

Source of variation	d.f.	Sum of squares %	Mean squares	Var. ratio	Signif. level
Mixtime	1	55·00	1·603815	455·07	>99
Starch	1	8·95	0·260846	74·01	>97·5
Size	1	22·95	0·669288	189·90	>99
Pressure	2	10·35	0·150970	42·83	>97·5
Mixtime. Starch	1	0·07	0·001958	0·55	
Mixtime. Size	1	0·47	0·013678	3·88	
Starch. Size	1	0·26	0·007692	2·18	
Mixtime. Pressure	2	0·05	0·000710	0·20	
Starch. Pressure	2	0·03	0·000424	0·12	
Size. Pressure	2	1·06	0·015515	4·40	
Mixtime. Starch. Size	1	0·27	0·008009	2·27	
Mixtime. Starch. Pressure	2	0·17	0·002502	0·71	
Mixtime. Size. Pressures	2	0·02	0·000289	0·08	
Starch. Size. Pressure	2	0·10	0·001448	0·41	
Residual	2	0·24	0·003524		
Total	23	100·00	0·126784		
Grand total	23	100·00			
Grand mean	0·841				
Total number of observations	24				

Effect on tensile fracture stress (MNm^{-2}) attributable to factors.

5a	Mixtime (min)	1	5	
		1·099	0·582	
5b	Starch (%)	1	7	
		0·945	0·737	
5c	Size (μm)	−20	+20	
		1·008	0·674	
5d	Compaction pressure (MNm-2)	100	150	200
		0·690	0·874	0·959

Table 6. ANOVA table based on time for 90% dissolution.

Source of variation	d.f.	Sum of squares %	Mean squares	Var. ratio	Signif. level
Mixtime	1	0·22	16·85	1·43	
Starch	1	64·22	4883·25	416·30	>99
Size	1	13·78	1047·55	89·30	>97·5
Pressure	2	0·79	30·02	2·55	
Mixtime. Starch	1	0·05	3·50	0·29	
Mixtime. Size	1	0·27	20·30	1·73	
Starch. Size	1	8·33	633·08	53·97	>97·5
Mixtime. Pressure	2	0·48	18·24	1·55	
Starch. Pressure	2	0·63	24·05	2·05	
Size. Pressure	2	2·33	88·49	7·54	
Mixtime. Starch. Size	1	5·74	436·84	37·24	>95
Mixtime. Starch. Pressure	2	0·79	29·89	2·54	
Mixtime. Size. Pressure	2	0·22	8·27	0·70	
Starch. Size. Pressure	2	1·86	70·53	6·01	
Residual	2	0·31	11·73		
Total	23	100·00	330·60		
Grand total	23	100·00			
Grand mean		22·91			
Total number of observations		24			

Effect on T90% (min) attributable to factors and interactions.

6a	Starch (%)		1	7		
			37·17	8·64		
6b	Size (μm)		−20	+20		
			29·51	16·30		
6c	Size (μm)		−20	+20		
	Starch (%)	1	48·91	25·43		
		7	10·11	7·17		
6d	Starch (%)		1		7	
	Size (μm)		−20	+20	−20	+20
	Mixtime	1	44·95	31·83	13·91	4·28
	(mins)	5	52·88	19·02	6·31	10·06

used in the larger drug particle size fraction for crystal fracture rather than bonding. It should be noted that the drug particle size as a factor in this study is, of necessity, a combination of the original particle size and any changes in drug particle size due to the compaction process. An alternative possibility is that the smaller drug size fraction may fill the interstitial pores in the tablet matrix whereas the larger fraction does not. This would result in more cohesive (Avicel–Avicel) bonds being formed with the smaller fraction and a reduced probability of crack propagation resulting in an increase in tablet strength.

The effects of starch concentration on fracture stress are shown in Table 5b. This is of lower significance (Table 5) than the mixing time or the drug particle size but is probably due to a similar phenomenon. The increased number of starch particles in the tablet when the starch concentration is increased, or correspondingly the reduced number of Avicel particles, means that the number of cohesive bonds formed on compaction is decreased resulting in a reduction of the tablet strength.

The effects of compaction pressure on fracture stress are significant at the 97·5% level (Table 5) and the mean effects attributable to compaction pressure are shown in Table 5d. The increase in tablet strength with increasing pressure is due to an overall increase in bonding due to closer particle to particle proximity during compaction.

The lack of any significant interactions between the mean factors (Table 5) tends to indicate that they are operating independently at the levels chosen, the fracture stress of a given trial being the cumulative effect of the main factors.

The ANOVA Table (Table 6) using T90% as the experimental determinant shows that the most significant effects, as might be expected, come from increasing the starch concentration, although the effects of the drug particle size are significant at the 97·5% level. Tables 6a and b respectively show the relative magnitudes of the mean T90% attributable to these single factors. However a closer examination of Table 6 indicates a significant (97·5%) interaction between the drug particle size and starch concentration factors. Table 6c gives a more detailed

analysis of the interaction where it is apparent that the drug particle size has an appreciable effect only at the lower starch concentration. Fig. 1 illustrates this point by showing the mean dissolution profiles for trials 6, 12, 18 and 24. These trials were all made at the same compaction pressure and with the same mixing time, but represent the four possible combinations of starch concentration and drug particle size. The profile of trial 6 (low starch, large size) is similar to the profiles of trials 12 and 24 (high starch) but markedly different from trial 18 (low starch, small size), thus it can be seen that the effect of increasing the drug particle size can be almost as great as increasing the starch concentration. It should be noted that the data expressed by Fig. 1 represent only part of the experiment, whereas Table 6c takes all of the experimental data into account.

The longer T90% (Table 6b) for paracetamol of smaller particle size is indicative of a decreased effective surface area relative to the larger particle size fraction. Normally a reduction in particle size results in an increased dissolution rate (Noyes & Whitney 1897); however the reverse has also been demonstrated for acetylsalicylic acid and phenacetin powders (Finholt 1974). The explanation for this behaviour is associated with the hydrophobic nature of the surface producing a decrease in the wetting rate. In the present study the wetting rate was probably not important due to the proximity of the other excipients. This is supported by Finholt's (1974) further work where he demonstrated that the effect of the particle size of the two drugs in granules was to increase the dissolution rate with decreasing size. The effect of drug particle size in the study presented here may be explained in two ways, both of which relate to the effects of drug particle size on tensile fracture stress. If crystal fracture does occur on compaction of the larger size fraction as postulated above, then it also follows that a new drug surface is produced at the same time. This would result in an increased effective drug surface area, that is, surface not coated with hydrophobic magnesium stearate, and a consequent increase in the dissolution rate.

A simpler explanation might be that a reduced tensile fracture stress with the larger drug size fraction results in a greater susceptibility to disintegration or surface erosion of the tablet. If this were the case then a correlation between dissolution and tensile fracture stress should be apparent. The intuitively appealing approach of using a linear regression analysis is not appropriate here because of

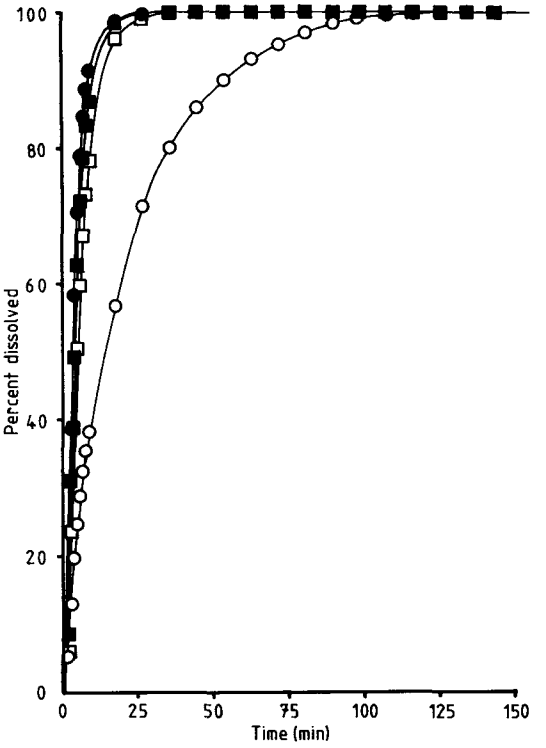

FIG. 1. Mean dissolution profiles for trials 6 (□), 12 (■), 18 (○) and 24 (●) showing the effect of low (□, ○) and high (■, ●) starch levels and small (○, ●) and large (□, ■) drug particle size.

the lack of homogeneity of the variance of both variables. However, if the ANOVA Table for T90% is recalculated with the effects of tensile fracture stress removed as a covariant, then the extent to which T90% is influenced by tensile fracture stress can be determined from the reduction in the percentage sum of squares. This analysis indicates that 81·8% of the variability in T90% is accounted for by the tensile fracture stress. This supports the explanation that changes in tensile fracture stress strongly influence changes in T90%.

It can be seen that mixing time by itself is not a significant factor (Table 6) in determining T90%, but the complex interaction of starch, size and mixing time is significant at the 95% level. The attributable effects of these factors are shown in Table 6d. As might be expected from the discussion above, very little effect of either drug particle size or mixing time is shown at the higher starch concentration. At the lower starch concentration the effect of increasing the mixing time is an increase in T90% with the smaller drug particle size, but a decrease in T90%

Table 7. ANOVA table based on dissolution rate constant.

Source of variation	d.f.	Sum of squares %	Mean squares	Var. ratio	Signif. level
Mixtime	1	0·00	0·000019	0·00	
Starch	1	52·61	0·382790	80·61	>97·5
Size	1	7·02	0·051060	10·75	>90
Pressure	2	3·24	0·011770	2·47	
Mixtime. Starch	1	0·90	0·006514	1·37	
Mixtime. Size	1	8·77	0·063798	13·43	>90
Starch. Size	1	1·83	0·013292	2·79	
Mixtime. Pressure	2	0·03	0·000125	0·02	
Starch. Pressure	2	3·19	0·011616	2·44	
Size. Pressure	2	0·74	0·002699	0·56	
Mixtime. Starch. Size	1	17·27	0·125686	26·46	>95
Mixtime. Starch. Pressure	2	0·74	0·002684	0·56	
Mixtime. Size. Pressure	2	2·12	0·007705	1·62	
Starch. Size. Pressure	2	0·24	0·000873	0·18	
Residual	2	1·31	0·004749		
Total	23	100·00	0·031635		
Grand total	23	100·00			
Grand mean		−0·199			
Total number of observations		24			

with the larger drug size. The decrease in T90% with increased drug particle size is apparent at both mixing times but is much greater with a longer mixing time. This effect cannot be explained simply, but tends to indicate that when the drug particle size is altered another mechanism is influencing the dissolution process. Further studies relating mixing time and drug particle size at low starch concentrations would be needed to understand this mechanism. This serves to illustrate the value of a factorial design experiment in that the effect of starch concentration can be seen to be the dominant factor affecting T90% in this formulation. However, at lower starch concentrations the effect of drug size becomes important, and indications are present that mixing time could become important if the effect of drug particle size were reduced.

The choice of the experimental factors, their levels and the experimental determinant are of critical importance, and preliminary investigations or past experience should be used to select likely factors to study. The levels of the factors should be equally carefully chosen to be well spaced within normal limits e.g. starch concentrations of 45 and 50% would obviously be inappropriate. Likewise the experimental determinant should be chosen to reflect the tablet requirements. For example if the ability of the tablet to resist abrasion during coating is important then the most appropriate determinant would probably be friability. If there is a compendial requirement for 75% drug release in 30 min, the appropriate determinant would be T75%. As an illustration of this the ANOVA Table using the dissolution rate constant [ln (100% dissolved) against time] is included (Table 7). A regression analysis of the data up to 99·8% dissolved gives lines with a correlation coefficient greater than 0·975. However the most significant factors show a slightly different order to those of the T90% (Table 6) (T50% and T60% show the same effects as T90% but are not included here). This may lead to erroneous conclusions as to the dominant mechanisms influencing the dissolution of a tablet. In this case Wagner (1969) has elucidated the error by suggesting that the validity of the dissolution rate constant as a method of expressing dissolution data should be restricted to those cases where the regression line passes through ln (100%) at zero time; with some of these trials this was not the case.

Conclusions

Factorial design of an experiment has been shown to be an efficient way of analysing the complex interactions involved in a complete tablet formulation and indicating the significant factors for detailed study.

The tensile fracture stress of a model paracetamol direct compression formulation containing a lubricant has been shown to be dependent mainly on mixing time probably by the mechanism elucidated by Bolhuis et al (1975). The effects of drug particle size, starch concentration and compaction pressure have all been shown to influence fracture stress at the levels chosen, with pressure being of least significance.

The T90% of the formulation has been shown to be mainly dependent on the concentration of starch, although alteration of the drug particle size also has an effect, particularly at low starch concentrations.

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