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Effects of interacting variables on the tensile strengths and disintegration times of paracetamol tablets

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The effects of separately varying the packing fraction (P), the proportions of microcrystalline cellulose, Avicel (A) and alginic acid, disintegrant (D), on both the tensile strengths and disintegration times of paracetamol tablets are in the order P ≫ A ≫ D. The combined effects of these variables on both tensile strength and disintegration time are A × P ≫ D × P > A × D.

Pharmaceutical tablets may contain several different ingredients whose proportions determine the mechanical properties of the tablets and their disintegration and dissolution characteristics. Processing variables such as granulation, temperature, rate of compression and packing fraction achieved can also affect the properties of the tablets. Several workers have studied the separate (Levy et al 1963; Chalmers & Elworthy 1975; Esezobo & Pilpel 1976) and combined (Kurup & Pilpel 1977; Adeyemi & Pilpel 1983; Sanderson et al 1984) effects of formulation and processing variables with the objective of optimizing the production and therapeutic performance of various tablet formulations.

The aim of the present study has been to determine how packing fraction and the addition of microcrystalline cellulose (Avicel) and alginic acid to paracetamol, separately and in combination, affected the tensile strengths and disintegration times of the resulting tablets.

Materials and methods

Paracetamol powder (mean projected diameter 7·7 μm) and microcrystalline cellulose (Avicel PH 101, mean projected diameter 16·8 μm measured by microscopy) were mixed together in different proportions as previously reported (Bangudu & Pilpel 1984). The mixtures were granulated through a 16 mesh sieve using distilled water and the rather fragile granules were dried at 60 °C for 12 h until their moisture content was <2% w/w as measured on an infra-red vacuum moisture tester (Townson and Mercer Ltd, Croydon). Various amounts of powdered alginic acid HED (Alginate Industries) which had been passed through a 100 mesh sieve were mixed with the granules which were then tableted at the rate of 40 min^{-1} on a single punch (Manesty F3) machine using a 10 mm diameter die, flat faced punches and different compression pressures in order to achieve packing fractions between 0·8 and 0·9. It was found unnecessary to use a lubricant which might otherwise have complicated interpretation of the test results. The tensile strengths of the tablets (after storing for 24 h over silica gel in a desiccator) were measured by diametral compression (Fell & Newton 1970) and their disintegration times by the standard BP method (1973) using four replicates. Reproducibility of results was generally to within ±2%.

Experimental design. Experiments were performed in a factorial design. Each of the three variables, packing fraction, proportion of Avicel and proportion of alginic acid was employed at a 'low' level (denoted by subscript L), a 'medium' level (subscript M) and a 'high' level (subscript H), see Table 1. (These were arbitrarily selected for convenience and it is recognized that the results of the analysis will depend on their absolute values.) Additional data were also obtained for samples containing 75% of Avicel.

Table 1. Levels of variables.

Variable	'Low' level	'Medium' level	'High' level
Packing fraction	0·80	0·85	0·91
% w/w Avicel	20	30	50
% w/w Alginic acid	1·0	2·0	3·0

By grouping the results into a number of sets it was possible to assess the effect that each variable had had separately on the properties of the tablets and also to determine the extent of interaction, if any, between any two variables (Woolfall 1964). This method is useful for deciding quickly whether a fuller and more detailed analysis of variance is justified. The effects of increasing, say A from its 'low' level to its 'high' level on say, tensile strength was found by summing all tensile strength results from samples containing 'high' levels of A and subtracting the sum of the tensile strength results from the samples containing 'low' levels of A. That is

$$\tfrac{1}{4}[(A_HP_HD_H + A_HP_LD_H + A_HP_HD_L + A_HP_LD_L) - (A_LP_HD_H + A_LP_LD_H + A_LP_HD_L + A_LP_LD_L)]$$

A similar procedure was adopted for analysing the effects of P and D and for analysing the changes produced by going from a 'low' to a 'medium' level and from a 'medium' to a 'high' level (Adeyemi & Pilpel 1983).

To determine the extent of interaction between any two variables, say A and P (at 'low' and 'high' levels) on

* Correspondence.

say, tensile strengths, the procedure was to treat the results as follows:

$$\tfrac{1}{4}[(A_LP_LD_L + A_LP_LD_H + A_HP_HD_L + A_HP_HD_H) - (A_LP_HD_L + A_LP_HD_H + A_HP_LD_H + A_HP_LD_L)]$$

and similarly for the other combinations at other levels (Adeyemi & Pilpel 1983).

A result of zero indicated no interaction; departure from zero provided a quantitative measure of the amount of interaction (Woolfall 1964).

Results and discussion

As expected (Heckel 1961; York & Pilpel 1973; Kurup & Pilpel 1977) the tensile strengths and disintegration times of the tablets increased with packing fraction; at any particular P, between 0·80 and 0·91 they also increased with the Avicel content as illustrated typically in Fig. 1. Addition of alginic acid reduced the disintegration time to a minimum at about 2% w/w but had little effect on tensile strength, Fig. 2. These results follow logically from the known properties of Avicel as an excipient for improving compression and bond formation between drug particles (Lamberson & Raynor 1976; Esezobo & Pilpel 1977) and of alginic acid as a disintegrant which acts by swelling in water and rupturing the bonds (Khan & Rhodes 1972).

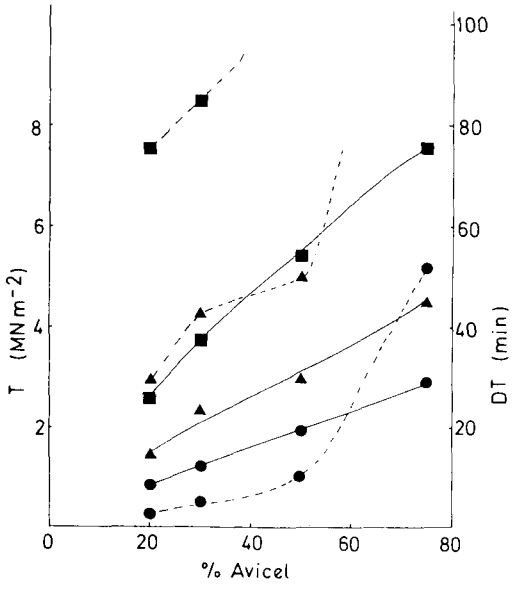

FIG. 1. Tensile strength, T and disintegration time, DT of tablets versus % composition of Avicel at different packing fractions, P and containing no alginic acid. Key: ——Tensile strength, – – – disintegration time, ● packing fraction 0·80, ▲ packing fraction 0·85, ■ packing fraction 0·91.

The relative effects of the variables at all three levels both on the tensile strengths and on the disintegration times of the tablets are P ≫ A ≫ D (Table 2). The packing fraction is a measure of the extent to which particles are brought together during consolidation to form bonds resulting in hard tablets. At any particular packing fraction, P it is known that the tensile strengths of different materials are comparable and do not differ by a factor of more than about 3 (Malamataris et al 1984). It is also known that the tensile strengths of materials increase exponentially with packing fraction (York & Pilpel 1973) so that a small increase in packing fraction has a large effect on tensile strength. This explains why increasing the packing fraction has a much

Table 2. Effect of packing fraction and composition on the tensile strength and disintegration time of tablets.

Effect on tensile strength (MNm^{-2}) of increasing from Low to High level of			Effect on disintegration time (min) of increasing from Low to High level of		
Packing fraction	Avicel	Alginic acid	Packing fraction	Avicel	Alginic acid
P	A	D	P	A	D
2·40	1·77	−0·11	60·75	29·75	−10·50
Low to Medium level of			Low to Medium level of		
Packing fraction	Avicel	Alginic acid	Packing fraction	Avicel	Alginic acid
P	A	D	P	A	D
0·80	0·53	−0·05	11·55	−4·45	−6·80
Medium to High level of			Medium to High level of		
Packing fraction	Avicel	Alginic acid	Packing fraction	Avicel	Alginic acid
P	A	D	P	A	D
2·04	1·02	−0·06	55·43	35·08	−1·58

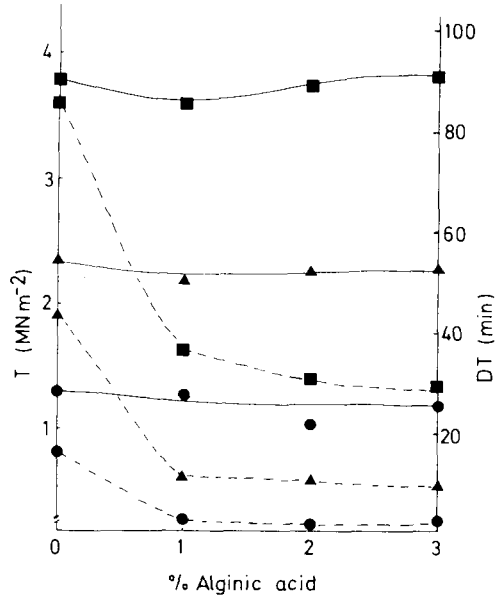

FIG. 2. Tensile strength, T and disintegration time, DT of tablets versus % composition of alginic acid at different packing fractions, P and containing 30% w/w Avicel. Key —— Tensile strength, – – – disintegration time, ● packing fraction 0·80, ▲ packing fraction 0·85, ■ packing fraction 0·91.

Table 3. Interaction coefficients.

Transitional level	Interaction coefficient for tensile strength (MNm^{-2}) between			Interaction coefficient for disintegration time (min) between		
	Avicel and Alginic acid	Avicel and Packing fraction	Alginic acid and Packing fraction	Avicel and Alginic acid	Avicel and Packing fraction	Alginic acid and Packing fraction
Low–High	0·04	0·71	−0·08	1·00	29·75	−9·00
Low–Medium	0·05	0·21	0·05	5·80	−2·55	−4·20
Medium–High	−0·22	0·44	−0·15	−5·58	35·93	−8·93

larger effect on tensile strength (and incidentally on disintegration time which is known to be directly related to it) than changing the amount of Avicel or alginic acid that has been incorporated in the mixture. Since the disintegration time is directly related to the tensile strength, for reasons which have been given elsewhere (Kurup & Pilpel 1977) the same argument applies to the greater effect of packing fraction P on disintegration times than those of A and D.

The greater effect of the proportion of A than that of D on both tablet properties is consistent with the use of Avicel as a tablet excipient for improving the compressibility of materials and producing strong, hard tablets. Their rate of disintegration appears to depend primarily on their hardness and on the rate at which water can penetrate them and rather less on the amount of alginic acid present as a disintegrant. It should be mentioned that Avicel itself has some disintegrant properties and this tends to complicate interpretation of the results.

Table 3 shows that the three variables are also interacting with each other at the three levels employed. The ranking order of the interactions for both tablet parameters is $A \times P \gg D \times P > A \times D$. It would be expected that the combined effect of any two variables would depend to some extent on their separate effects and since we have already seen these are in the order $P \gg A \gg D$ the above result seems reasonable.

It is hoped that this type of analysis on the separate and combined effects of variables will prove useful in the future development of commercial tablet formulations.

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