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COMMUNICATIONS

The effects of interacting variables on the tensile strength, disintegration and dissolution of paracetamol tablets

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Abstract—A factorially designed scheme has been used to analyse the separate and combined effects of packing fraction (P), nature of binder (N) and concentration of binder (C) on the tensile strength, disintegration and dissolution (t50%) times of paracetamol tablets. In general, P has the greatest effect on tensile strength, disintegration and dissolution times followed by C then N. For the variables in combination, the ranking of the effects on tensile strength, for the PVP/gelatin formulations, are $P \times N > N \times C > P \times C$ and for the PVP/tapioca formulations are $P \times C = N \times C > P \times N$. For disintegration and for dissolution, the ranking for the PVP/gelatin formulations are $P \times C > P \times N = N \times C$ and $P \times N > P \times C > N \times C$, respectively, and for the PVP/tapioca formulations are $P \times N > N \times C = P \times C$. The results also show that tapioca acts as a binding agent when included in paracetamol tablet formulations, but it is a weaker binder than either PVP or gelatin. It is thus required in a higher concentration to produce tablets of comparable physical properties with those formulated with PVP or gelatin.

Previous investigations (Ahmad & Pilpel 1967; Sakr et al 1972; Davies & Gloor 1972; Esezobo & Pilpel 1976) have shown on a qualitative basis, that the compression pressure, type and concentration of binders have profound influence on the physical properties of compressed tablets.

In the present work, we have carried out a quantitative assessment on how the above three formulation factors affect the tensile strength, disintegration and dissolution of paracetamol tablets by employing factorially designed experiments using a three-way analysis of variance to determine the effects and extent of interaction between the three variables at two levels on the properties of tablets.

This type of analysis has been employed by various workers (Fonner et al 1970; Dincer & Ozdurmus 1977; Plaizier-Vercammen & De Neve 1980; Adeyemi & Pilpel 1984) and has been shown to be relevant to formulation and assessment of pharmaceutical systems.

Two of the three different types of binders compared are well known (i.e. PVP and gelatin). The third, tapioca, is the dried fibrous remnant material obtained by the removal of a large percentage of starch from cassava (*Manihot utilissima*)—a local starchy root obtained from Nigeria and used extensively as food. Although its use in pharmaceutical tablet formulations has not been widely reported, it is used in the preparation of some baby foods. Being a material from a starchy source, it is reasonable to assume that it may have some binding properties when included in tablet formulations. This is because preliminary work showed that it has the property of absorbing water, swelling and forming a mucilaginous mass in the presence of water.

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Materials and methods

The materials used were paracetamol powder BP (Cambrian Chemicals, UK); microcrystalline cellulose, Avicel PH101, (Honeywell and Stein Ltd. UK) polyvinylpyrrolidone, PVP, mol. wt 44 000 and potato starch (BDH Chemicals Ltd, Poole UK), gelatin IP (Chemical and Instrument Corp; Calcutta) and tapioca prepared from Nigerian cassava with a mean projected particle diameter of 15 μm.

All other materials were of good laboratory grades.

Preparation of granules. Batches (40 g) of mixtures of paracetamol (mean projected diameter 8·2 μm) (70% w/w), Avicel (mean projected diameter, 16·7 μm) (20% w/w) and potato starch (10% w/w) were dry mixed for 5 min in a Kenwood planetary mixer and then moistened either with 29 mL of distilled water or with appropriate amounts of PVP or gelatin solutions or tapioca mucilage, to produce granules containing varying concentrations of the different binding agents. Massing was continued for 3 min and the wet masses were granulated by passing them manually through a No 10 mesh sieve, dried in a hot air oven for 18 h at 70°C and then resieved through a No 16 mesh sieve.

The moisture content of the granules, which ranged between 2·0 and 2·2% w/w, was determined with a vacuum moisture tester (Townson & Mercer Ltd; Croydon, England). Particle densities of the formulations were determined using a Beckmann air comparison pycnometer (Model 930, Beckmann Instruments, California, USA).

Preparation of tablets. Tablets of 500 mg were prepared from the 355–710 μm size fraction of granules by compressing them for 1 min with preselected pressures at a rate of 0·22 mm s^{-1} using a hand press fitted with a pressure gauge reading up to 5 tons (Research and Industrial Instruments Co: London). Before each compression, the die (10·5 mm diameter) and the flat-faced punches were lubricated with a 1% w/v dispersion of magnesium stearate in acetone. After ejection, the tablets were stored in air tight containers to allow for hardening and elastic recovery before measurements were carried out on them.

The dimensions and the weights, Wg, of the tablets were determined to within 0·01 mm and ±1 mg and their packing fractions, P, were calculated using the equation;

$$P = \frac{W}{V_t P_s} \quad (1)$$

where V_t = volume of tablet (cm^{-3}), and P_s = particle density of the powder or mixture ($g\ cm^{-3}$)

Tensile strength test. The tensile strengths of the tablets were determined by diametral compression (Fell & Newton 1970) using a CT 40 tester (Engineering System, Nottingham) and applying the equation,

$$T = \frac{2L}{Dt} \quad (2)$$

where T = tensile strength (Nm^{-2}), L = load in Newton causing failure, D = tablet diameter (m), t = tablet thickness (m).

Disintegration and dissolution tests on tablets. The disintegration times were measured individually on 10 tablets from each batch in distilled water at 37±1°C using the BP 1973 method and a Manesty Disintegration Tester, and an average calculated.

The dissolution rates were determined at the same temperature in 1 L of standard pH2 buffer solution (BP 1973) in a round-bottomed flask employing a two-bladed paddle fitted 2 cm below the surface of the liquid, stirring at 100 rev $min.^{-1}$ The amount of paracetamol that had dissolved in the medium after a certain period was determined by measuring the absorbance at 249 nm with a spectrophotometer (Cecil Instruments Ltd., Cambridge, UK), replacing the sample by an equal volume of pH2 buffer solution at the same temperature to keep the volume of the dissolution medium constant. All measurements were made in triplicate and the results given are the means of several determinations.

These results were subjected to a three-way analysis of variance to determine the effects on the tensile strengths, disintegration and dissolution (t50%) times of the three variables; packing fraction (P) nature of binding agent (N) and concentration of binding agent (C). These variables were selected at high (denoted by the subscript, H), and low (by subscript, L) levels.

Results

Fig. 1 is a representative graph of tablet tensile strength versus packing fraction for PVP binder at different concentrations.

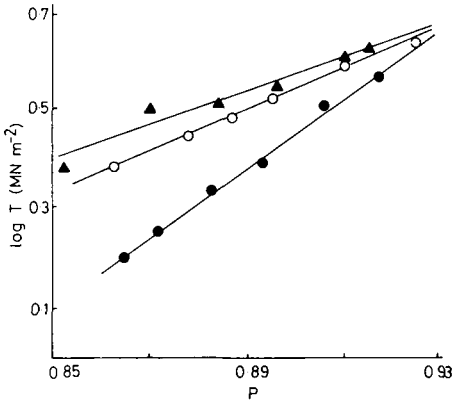

FIG. 1. Log tensile strength (T) versus packing fraction (P) for tablets containing 0–5% w/w PVP. ▲5% w/w PVP. O 2·5% w/w PVP. ● 0% w/w PVP.

They all fitted the general equation

$$\text{Log } T = A\ P_f + B \quad (3)$$

with a correlation coefficient > 0·97. A and B are constants which depend on N and C.

The values of the tensile strengths of all the tablets at fixed packing fractions of 0·87 and 0·92 (selected because they involved minimum extrapolation of the rectilinear plots of log T vs P_f) were calculated by regression analysis and are listed in Table 1. It can be seen that the tensile strengths increased as the packing fraction and binder concentration, were increased. At the same packing fraction and binder concentration, tablets formulated with gelatin and PVP had approximately the same tensile strengths and they were higher than for those formulated with tapioca.

Table 1. Values of tensile strength, disintegration, dissolution (t50%) for the tablets at packing fractions of 0·87 and 0·92.

Binder type	Concn of binder (% w/w)	Tensile strength (MNm^{-2})		Disintergration time (min)		Dissolution (t50%) (min)	
		Packing fraction (P)					
		0·87	0·92	0·87	0·92	0·87	0·92
Gelatin	0	1·70	3·89	0·50	1·50	9·50	21·00
	2·5	2·30	4·32	1·00	12·00	29·50	44·50
	5	2·80	4·79	8·00	43·00	32·75	52·00
PVP	2·5	2·51	4·27	1·00	9·50	15·50	38·50
	5	2·92	4·47	3·25	45·00	20·00	45·00
Tapioca	2·5	1·78	3·72	0·50	2·00	12·50	18·00
	5	2·19	4·47	0·75	4·00	13·50	20·00
	10	2·69	4·90	1·00	12·50	22·50	32·00

The disintegration results for the tablets were plotted as functions of packing fraction for the various binders (N) and at different values of C and are illustrated in Fig. 2 for tablets formulated with tapioca binder. It can be seen that the disintegration times increased as the packing fraction and binder concentration were increased.

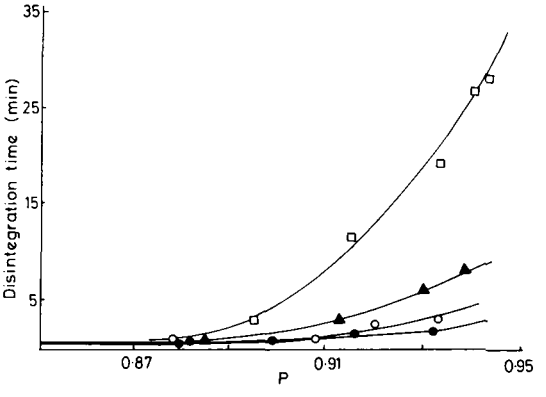

FIG. 2. The effects of packing fraction (P) and binder (tapioca) concentration on the disintegration time of paracetamol tablets. □ 10% w/w tapioca. ▲ 5% w/w tapioca. O 2·5% w/w tapioca. ● 0% w/w tapioca.

Table 1 shows that at packing fractions of 0·87 and 0·92 the disintegration times increased with increasing C. At the same P and C, tablets formulated with gelatin had the longest disintegration times followed by those formulated with PVP while those

formulated with tapioca binder had the shortest disintegration times.

The dissolution results were obtained in the form of plots of cumulative percentage paracetamol dissolved versus time and typical plots for 5% w/w tapioca binder at different packing fractions are shown in Fig. 3. From these plots the values of

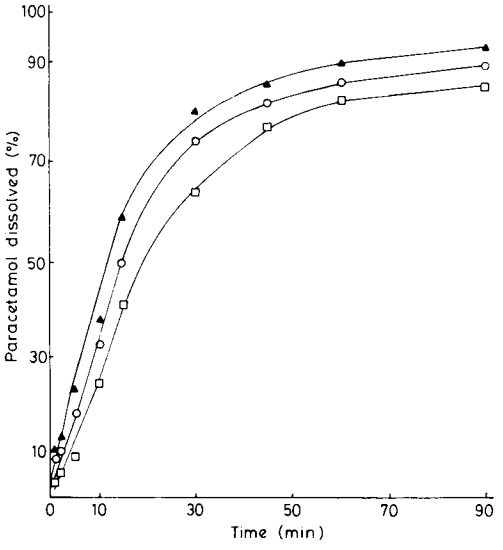

FIG. 3. Effect of packing fraction (P) on the dissolution profiles of paracetamol tablets containing 5% w/w tapioca. □ 0·920. ○ 0·880. ▲ 0·857.

t50% (the time required for 50% of the paracetamol to be released) were obtained and plotted against packing fraction in Fig. 4. From Table 1, it can be seen that the t50% values for the tablets increased as the values of P and C increased. At the same values of P and C, tablets formulated with gelatin had the highest t50% values followed by those made with PVP and then by those made with tapioca.

Discussion

The procedure for calculating the independent and interacting coefficients is given in Appendix 1 and the results are in Table 2. It can be seen that the individual effects of the variables on the

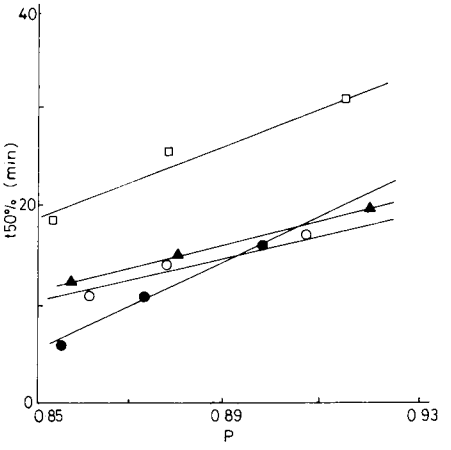

FIG. 4. The effects of packing fraction (P) and binder (tapioca) concentration on the time required for 50% of the paracetamol to be released. Symbols as in Fig. 2.

tensile strengths, disintegration and dissolution times of the tablets is generally ranked P > C > N.

An interaction between variables is described as 1st-order when the effect of changing the level of one is influenced by that of one other and 2nd-order when influenced by the level of two others. From Table 2 it is seen that P, N and C interact with each other to varying extents to alter the tensile strengths of the tablets. P and N interact more than N and C while P and C showed little interaction. Similar results were obtained for formulations containing either PVP or tapioca. Table 2 also shows that for PVP/gelatin formulations the interacting effects of P and C had greater influence on the disintegration time than either P and C or N and C. For the PVP/tapioca formulations the interacting effects of all the variables influenced the disintegration time to a larger extent as shown by their relative large interaction coefficients. The interacting effect of P and N as well as that of N and C decreased the disintegration time of tablets probably due to the weaker binding property of tapioca when compared with PVP.

The interaction coefficients in Table 2 also show that the interaction between P and N and between N and C produced decreasing effects on dissolution times while that between P and C increased the dissolution times for all the formulations. The

Table 2. Quantitative effects of packing fraction (P), concentration of binder (C) and nature of binder (N) on tensile strength, disintegration and dissolution (t50%) of the tablets.

A. Employing PVP and gelatin as binder.

	Independent coefficient		
Variables	Tensile strength (MNm^{-2})	Disintergration time (min)	Dissolution (t50%) (min)
P	1·82	26·63	21·63
C	0·41	21·50	5·63
N	0·02	1·25	8·63

Interaction coefficient	First order interaction coefficient		
P × C	−0·025	16·75	1·875
P × N	0·22	−3·50	−4·625
N × C	0·055	−2·375	−0·125

B. Employing PVP and tapioca binder.

	Independent coefficient		
Variables	Tensile strength (MNm^{-2})	Disintergration time (min)	Dissolution (t50%) (min)
P	1·73	16·31	16·19
C	0·59	12·44	3·31
N	−0·35	−15·44	−15·06

Interaction coefficient	First order interaction coefficient		
P × C	−0·27	11·31	1·06
P × N	0·13	−13·81	−10·06
N × C	0·24	−11·44	−2·19

magnitude of this effect was observed to be greater for the PVP/tapioca system indicating a wider difference between the use of these two materials as binding agents when compared with PVP/gelatin formulations.

The effects of P, N and C on tensile strength are shown in Fig. 1 and Tables 1 and 2. It is seen that as P increases the tensile strength of the tablet increases due to the mechanism of asperity melting. During tableting, high pressures exist at the minute contact points between particles where pressure is transmitted. In addition, the heat of interparticle friction is generated at these points and this combination of high pressure and high temperatures provides the necessary conditions for asperity melting for subsequent bonding to occur. This mechanism would be expected to contribute to the strength of tablets (York & Pilpel 1972; Pilpel & Esezobo 1977; Esezobo & Pilpel 1986) and should therefore be considered when tablets of specific strengths are required.

As for the effects of N, gelatin produced tablets of slightly higher strength than PVP at the same P and C. The relatively low value of the independent coefficient obtained for N (see Table 2) suggests that the difference in the binding effects of PVP and gelatin is insignificant, hence either of these two binders may be used in paracetamol tablet formulation. However, a change from the use of PVP to tapioca caused a decrease in the tablets' tensile strength. Thus, tapioca is a weaker binder than either PVP or gelatin. This may be ascribed to tapioca's low plasto-elastic properties. Therefore, a higher concentration of tapioca is required to produce tablets of acceptable mechanical strength.

Considering C, Fig. 1 and Table 1 show that increases in binder concentration produced systematic increases in the tensile strength of the tablets. This is in agreement with previous observations made on other formulations (Esezobo & Pilpel 1976; Kurup & Pilpel 1979).

Turning next to the disintegration and dissolution (t50%) times, P has the biggest effect and increasing P increases both times (see Fig. 2, Table 2). This could be ascribed to the reduction in the size of capillary spaces between the particles due to bond formation, which prevented the easy penetration of water through the tablets. Increasing C also increases markedly the disintegration and dissolution times and this is because binders are forced into interparticular spaces, thereby increasing the area of contact between particles leading to the formation of additional solid bonds. The increases in disintegration and dissolution times of the tablets produced by increasing P and C is as expected since high pressures during tableting and increasing binder concentration produce welded bonds and therefore strong and impervious tablets. Thus, the magnitudes of P and C employed in the formulation of tablets need to be carefully chosen to enable the production of tablets which will disintegrate and dissolve in good time.

Considering N, a change from PVP to gelatin increases the disintegration and dissolution times of the tablets while a change from PVP to tapioca reduces the disintegration and dissolution times (see Tables 1, 2). This is as expected since gelatin forms a dry film round the granules; this dried film must be rehydrated since it forms a barrier to the diffusion of water and drug molecules. This will thus prolong the disintegration and dissolution times of the tablets. As for PVP, although it forms a film, its rate of rehydration is faster because its film is more water soluble than that of the gum. Tapioca produces the shortest disintegration and dissolution times as expected since it produces tablets of weaker strength than PVP or gelatin.

Appendix 1

Calculation of independent coefficient

In the present work, packing fraction is denoted by P, nature of binding agent by N and concentration of binding agent by C.

The experimental design was based on using each of the variables at a "high" and "low" level (denoted by subscripts H and L, respectively). Thus, the number of experiments required in the design was 2^3(i.e. 8). The possible combinations between the variables were:

$$P_H N_L C_L,\ P_H N_H C_L,\ P_H N_L C_H,\ P_H N_H C_H,\ P_L N_L C_L,\ P_L N_L C_H,\ P_L N_H C_L \text{ and } P_L N_H C_H.$$

where, for comparing two binders, P_H = high packing fraction (0·92), P_L = low packing fraction (0·87), N = nature of binder, where, in one case (PVP/gelatin) subscript L is PVP, subscript H is gelatin, in the other (PVP/tapioca) subscript L is PVP, subscript H is tapioca. C_H = high binder concentrations (i.e. 5% PVP or gelatin or tapioca) C_L = low binder concentration (i.e. 2·5% PVP or gelatin or tapioca).

By grouping the results from the combinations into a number of sets, it was possible to assess the effect that each variable had on the tensile strength, disintegration time or t50% dissolution time of tablets and also to determine whether the variables were interacting or acting independently of each other.

The effect of increasing, say, packing fraction from a "low" level to a "high" level on tensile strength, disintegration or dissolution rates was determined by summing all the results of these parameters for combinations compressed at "high" packing fraction and subtracting from it the sum of the results of combinations at "low" packing fractions.

The effects of the nature of binder and concentration of binder were calculated similarly.

Calculation of interaction coefficient

To determine whether there was any interaction between any two variables, the results of the combinations in which both appear together either at "high" or "low" levels were summed and the sum of all other combinations of the variables subtracted from this to obtain an interaction coefficient.

A result of zero from any of the derived expressions indicates no interaction between the variables. A result significantly removed from zero indicates an interaction occurring between the variables, the extent of which is determined by the magnitude of the interaction coefficient (Woolfall 1964).

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