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The effects of interacting variables on the tensile strength, disintegration and dissolution of oxytetracycline-lactose tablets

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Summary

A method is described for analyzing the separate and combined effects of particle size (D), percentage of lactose (P) and temperature (U), on the tensile strength, disintegration and dissolution (t_{100}) times of physically mixed and formulated oxytetracycline-lactose tablets.

U has the greatest effect on tensile strength, D has the greatest effect on disintegration, and P on dissolution time. For the variables in combination the orders of the effects on tensile strength are $P \times U > D \times P > D \times U$ for the physically mixed tablets and $D \times P > D \times U > P \times U$ for the formulated ones; the orders of the effects on disintegration and dissolution are $D \times P > D \times U \geqslant P \times U$ for both types.

Explanations are offered for the results in terms of the mechanisms involved in the formation, disintegration and dissolution of tablets.

Introduction

In a previous investigation (Adeyemi and Pilpel, 1983) it was shown that the tensile strengths of certain loosely packed (packing fraction 0.4) mixtures of oxytetracycline and lactose powders depended on the method of mixing the ingredients, either physically or by granulation, on the composition, particle size distri-

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bution of the mixtures and on the temperature of compression. Using an equation developed by Kočova and Pilpel (1973) it was found possible to predict the tensile strengths of certain other mixtures of these two powders with reasonable accuracy.

It has now been considered desirable to extend this work to tablets of the same mixtures by carrying out factorially designed experiments using a three-way analysis of variance to determine the effects and extent of interaction between the three variables at 3 levels on the properties of the tablets.

This type of analysis has been employed by various workers (Fonner et al., 1970; Dincer and Ozdurmus, 1977; Plaizier-Vercammen and de Nève, 1980) and has been shown to be relevant to formulation and assessment of pharmaceutical systems.

In the present work replicate measurements were made of tensile strength, disintegration and dissolution of tablets compressed to a packing fraction (P_f) of 0.82 (selected because it involved minimum extrapolation of tensile strength data and because it was representative of commercial tablets).

Materials and Methods

Materials

The materials used were the same as in the previous investigation; oxytetracycline dihydrate powder from I.C.I. Pharmaceuticals Division, E.P. 11 (1971) and lactose powder B.P. from Whey Products.

Batches of oxytetracycline and lactose were classified into size fractions 0–10, 10–20, 20–30 μm and were then mixed in various proportions to produce a range of physical mixtures. Further batches were wet granulated to produce formulated mixtures in the same proportions, the granules were dried, milled and classified into the same three size ranges as above. All the samples were stored as previously described. Their compositions, code numbers and physical properties have already been given (Adeyemi and Pilpel, 1983).

Preparation of tablets

Approximately 400 mg of each of the above mixtures was maintained at the required temperature between -10 and $+50\,^{\circ}C$ for 10 min and was then compressed at this temperature for 1 min with a predetermined load at a rate of 0.22 $mm \cdot s^{-1}$ using a thermostated hand-press (Research and Industrial Instruments, London), (Malamataris and Pilpel, 1981). The die (10.5 mm diameter) and the flat-faced punches were lubricated with a 1% w/w dispersion of magnesium stearate in chloroform. After ejection the tablets were stored over silica gel for 24 h for hardening and elastic recovery. Their weights and dimensions were then accurately measured and their packing fractions calculated (Kurup and Pilpel, 1977).

Testing

The tensile strengths of the tablets were measured at room temperature in triplicate by diametral compression using a CT 400 tester (Engineering System, Nottingham). It consisted of an upper flat horizontal plate driven downwards by a constant speed motor on to the tablet which was positioned on its edge on a lower

flat plate. The lower plate was connected through a rod to a digital scale which measured the force required to break the tablet. To ensure even distribution of stress across the tablets cardboard padding strips were placed on the upper and lower plates. For a flat-faced tablet,

$$T = \frac{2P'}{\pi D' t'} \quad (1)$$

where T is the tensile strength of the tablet, P′ is the force in MN. required to split it cleanly into two halves, D′ is its diameter in m and t′ is its thickness in m (Timoshenko and Goodier, 1951; Fell and Newton, 1970).

The disintegration times of the tablets were measured in distilled water at $37 \pm 1°C$ in a Manesty disintegration tester BP (1973). Tablets were considered completely disintegrated when all the particles passed through the wire mesh.

The dissolution rates were determined at the same temperature in 1 litre of standard pH 2 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 $rev \cdot min^{-1}$. The amount of oxytetracycline that had dissolved in the medium after a certain period was determined by measuring the absorbance at 353 nm with a Cecil CE202 spectrophotometer (Hiscox, 1951). (For tablets containing 100% w/w lactose, 1 litre of standard pH 6 buffer solution was used and the amount of lactose dissolved was determined by optical rotation in a polarimeter, Bellingham and Stanley). All measurements were made in triplicate or more and the results given were the mean of several determinations.

In order to measure the rate of water penetration into the tablets at room temperature, a standard drop of water was delivered on to each tablet from an Alga syringe at a constant distance from the tablet. The height in cm of the drop was measured using a cathetometer and the time (in s) taken by the drop to pass into the tablet was recorded. The tablet was covered to prevent evaporation of the drop during the measurement. The mean of 5 measurements was taken for each tablet.

These results were subjected to a three-way analysis of variance to determine the effects on the tensile strengths, disintegration and dissolution (t_{100}) times of the 3 variables particles size (D), percentage of lactose in the mixture (P) and temperature of compression (U). These variables were selected at high (denoted by the subscript H), medium (by subscript M) and low (by subscript L) levels. Thus D_H denotes the 20–30 μm size fraction, D_M the 10–20 μm fraction and D_L the 0–10 μm fraction: P_H denotes mixtures containing 75% lactose, P_M those with 50% lactose and P_L those with 25% lactose; U_H refers to results at 50 °C, U_M those at 20 °C and U_L those at −10 °C. The procedure for carrying out this analysis is described in Appendix 1.

Results

The tensile strength results on the tablets at different temperatures were similar to those obtained previously on the loosely packed powders in that at all temperatures

they fitted the general equation:

$$\log T = KP_f + B \quad (2)$$

with a correlation coefficient > 0.98. K and B were constants which depended on D, P and U and on how the mixtures had been prepared. Typical results to illustrate this behaviour are shown in Fig. 1A and B. The values of the tensile strengths of all the samples at a fixed packing fraction of 0.82 (selected because it 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 temperature of compression was increased but decreased as the particle size fraction and the proportion of lactose were increased; the tablets from formulated mixtures had higher tensile strengths than those from physical mixtures.

The disintegration results for the two types of tablets are plotted as functions of packing fraction for samples at a fixed value of U, various values of P, and at D = (0–10)μm in Fig. 2A and D = (20–30)μm in Fig. 2B. It can be seen that the disintegration times increased as the packing fraction was increased. Table 1 shows that at a fixed P_f of 0.82 the disintegration times decreased with increasing D and P

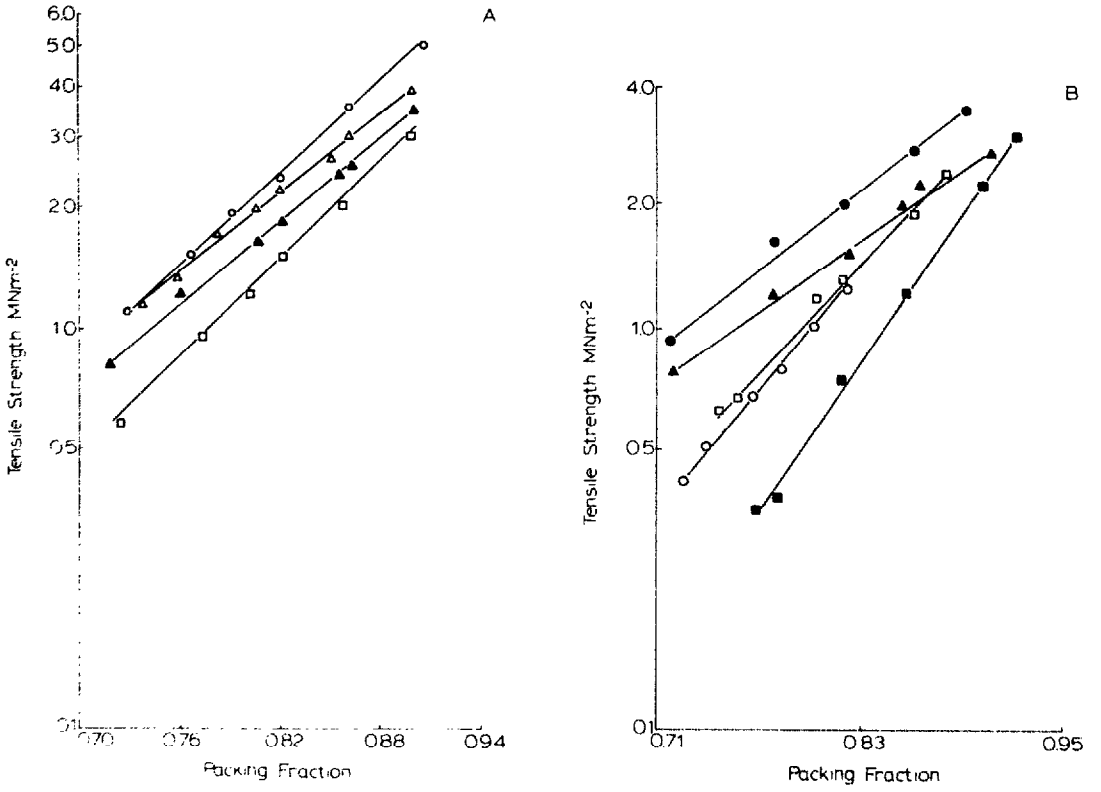

Fig. 1. A: log tensile strength versus packing fraction for tablets containing 0–50% (w/w) lactose compressed and tested at 20 °C; size 0–10 μm. △, oxytetracycline; ▲, M_1; □, M_2; ○, M_5. B: log tensile strength versus packing fraction for tablets containing 25–100% (w/w) lactose compressed and tested at 20 °C; size 10–20 μm. ○, lactose; ▲, M_1; □, M_2; ■, M_3; ●, M_4.

TABLE 1

VALUES OF TENSILE STRENGTH, DISINTEGRATION, DISSOLUTION (t_{100}) TIMES AND RATE OF WATER PENETRATION FOR PHYSICALLY MIXED AND FORMULATED TABLETS AT $P_f = 0.82$

Sample	Sample code no.	Particle size fraction (μm)	Tensile strength $MN \cdot m^{-2}$			Disintegration time (min)			Dissolution (t_{100}) time (min)			Rate of water penetration $(cm/s) \times 10^4$		
			Temperature of compression (°C)											
			−10	+20	+50	−10	+20	+50	−10	+20	+50	−10	+20	+50
Oxytetracycline	Y	0–10	1.28	2.26	3.16	*	*	*	386	400	426	2.41	2.0	1.6
		10–20	1.13	2.09	2.83	0.86	1.09	2.03	60.3	70	83.7	11.11	10.6	10.3
		20–30	1.08	1.85	2.32	0.49	0.63	1.08	5.10	8	10.2	17.36	17.0	16.5
Lactose	L	0–10	0.99	1.54	2.20	0.64	1.14	3.18	4.80	9.30	15.1	24.52	20.0	18.0
		10–20	0.65	1.21	1.84	0.45	0.89	1.69	3.20	7.40	13.0	56.10	50.7	48.6
		20–30	0.46	1.00	1.48	0.37	0.41	1.21	1.60	2.50	3.20	49.50	47.0	44.5
Physical mixtures														
Oxytetracycline 75% lactose 25%	M_1	0–10	1.27	1.79	2.98	7.90	10.5	13.71	52	60	71	2.25	2.0	1.7
		10–20	1.06	1.51	2.68	1.30	2.10	3.27	16.5	20	22.4	12.02	11.3	10.1
		20–30	1.00	1.38	2.05	0.46	0.82	1.32	2.4	3.5	5.0	14.10	13.0	12.6
Oxytetracycline 50% lactose 50%	M_2	0–10	1.18	1.54	2.65	2.02	3.16	5.60	6.80	10.0	13.50	3.10	2.9	2.0
		10–20	1.00	1.34	2.39	1.28	1.80	2.70	3.20	5.50	6.60	12.24	12.0	11.3
		20–30	0.92	1.05	1.70	0.36	0.56	1.00	0.85	2.00	3.50	24.24	20.0	19.7
Oxytetracycline 25% lactose 75%	M_3	0–10	0.91	1.01	2.23	0.86	1.41	3.01	1.70	2.00	3.80	5.20	4.8	3.9
		10–20	0.80	0.75	1.61	0.61	1.02	1.64	0.53	1.00	1.30	13.02	13.0	12.2
		20–30	0.33	0.50	1.31	0.31	0.45	0.75	0.41	0.70	1.00	27.80	27.0	26.2
Formulated mixtures														
Oxytetracycline 75% lactose 25%	M_4	0–10	2.0	2.38	3.97	28.80	33.0	36.5	124	130	138.6	7.04	7.7	6.8
		10–20	1.62	2.01	3.28	16.05	17.50	19.31	66.60	70.0	73.80	8.4	8.0	7.4
		20–30	1.41	1.89	2.79	3.72	6.80	8.20	26.80	30.0	33.30	7.11	6.8	6.4
Oxytetracycline 50% lactose 50%	M_5	0–10	1.80	2.30	3.46	24.3	26	30.35	39.40	45.0	46.4	9.2	8.5	8.0
		10–20	1.38	1.88	3.01	8.51	9.6	10.89	15.60	18.0	20.0	12.1	11.2	10.5
		20–30	1.18	1.49	2.58	2.05	2.2	3.70	1.22	2.0	4.5	16.0	16.1	15.0
Oxytetracycline 25% lactose 75%	M_6	0–10	1.63	1.89	2.69	15.38	18.2	19.76	4.82	6.0	11.1	10.4	9.3	8.8
		10–20	1.25	1.51	2.60	4.45	5.20	6.11	1.71	2.8	5	18.0	17.4	16.6
		20–30	0.56	0.71	2.01	1.20	1.80	2.70	1.02	2.0	3.60	25.0	24.0	23.2

* = Tablets that failed to disintegrate even after 2 h.

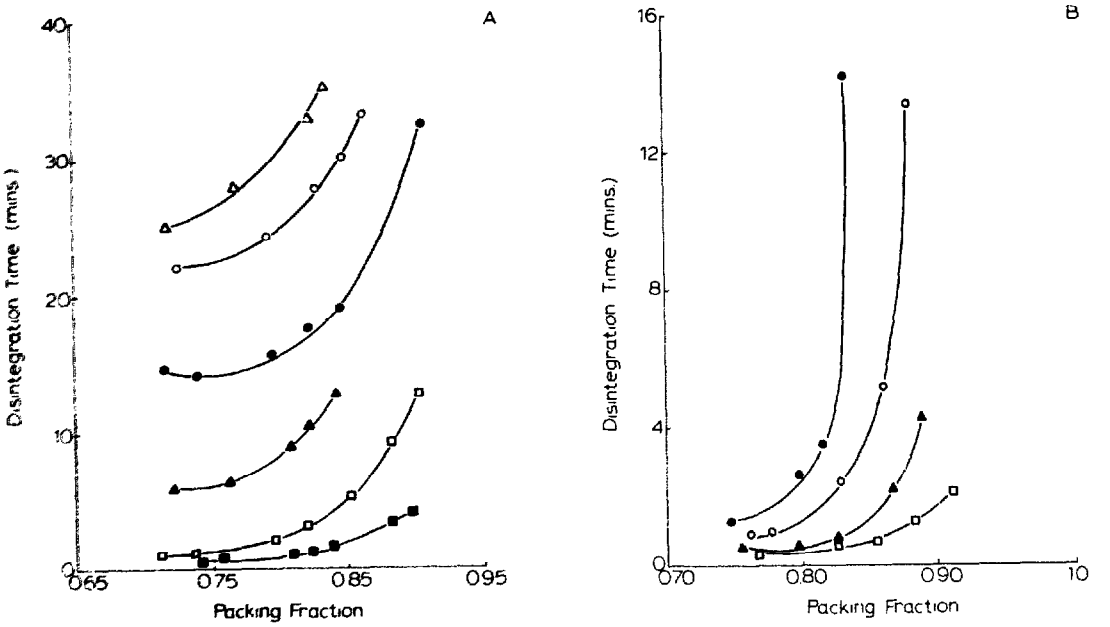

Fig. 2. A: The effects of proportion of lactose and packing fraction on the disintegration of oxytetracycline-lactose tablets compressed at 20 °C; size 0–10 μm. ▲, M_1; □, M_2; ■, M_3; △, M_4; ○, M_5; ●, M_6. B: the effects of proportion of lactose and packing fraction on the disintegration of oxytetracycline-lactose tablets compressed at 20 °C; size 20–30 μm. ▲, M_1; □, M_2; ●, M_4; ○, M_5.

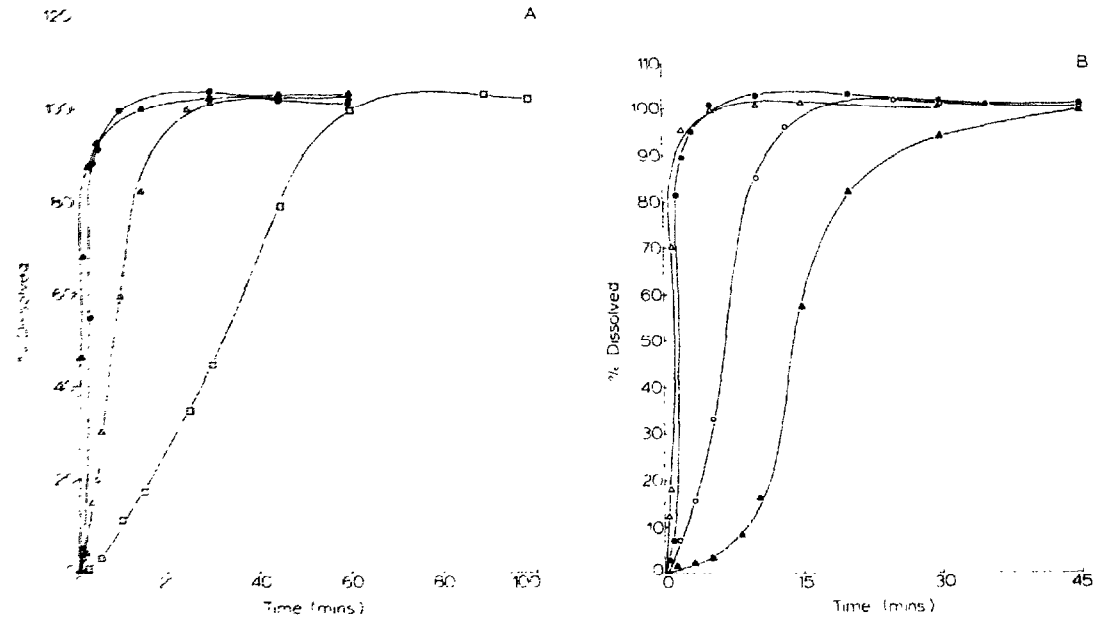

Fig. 3. A: effect of packing fraction on the dissolution profiles of tablets containing 25% and 50% (w/w) lactose of particle size fraction 0–10 μm compressed at 20 °C. △, M_1, $P_f = 0.763$; □, M_1, $P_f = 0.820$; ▲, M_2, $P_f = 0.739$; ●, M_2, $P_f = 0.819$. B: effect of packing fraction on the dissolution profiles of oxytetracycline tablets containing 25–75% (w/w) lactose of particle size fraction 20–30 μm compressed at 20 °C. ▲, M_4, $P_f = 0.820$; △, M_5, $P_f = 0.826$; ○, M_5, $P_f = 0.859$; ●, M_6, $P_f = 0.893$.

but increased with increasing U for both types of mixtures.

The dissolution results were obtained in the form of plots of cumulative percentage oxytetracycline dissolved versus time and typical plots for different levels of D and P at a constant U and different packing fractions are shown in Fig. 3A and B. From these plots the values of t_{100} (the time required for 100% of the oxytetracycline to be released) were obtained. From Table 1 it can be seen that at a fixed P_f of 0.82 the t_{100} values for both types of tablets decreased as the values of D and P were increased but increased with increasing U.

The dissolution equation of Noyes and Whitney (1897) is:

$$dc/dt = k(C_s - C) \tag{3}$$

where C_s is the concentration of the solute at saturation, C its concentration at time t and k is a dissolution rate constant. Eqn. 3 may be integrated to give:

$$\ln[C_s/(C_s - C)] = kt \tag{4}$$

The present dissolution results were analyzed by plotting $\ln[C_s/(C_s - C)]$ vs t following the method of Kitazawa et al. (1975) and either a single straight line of

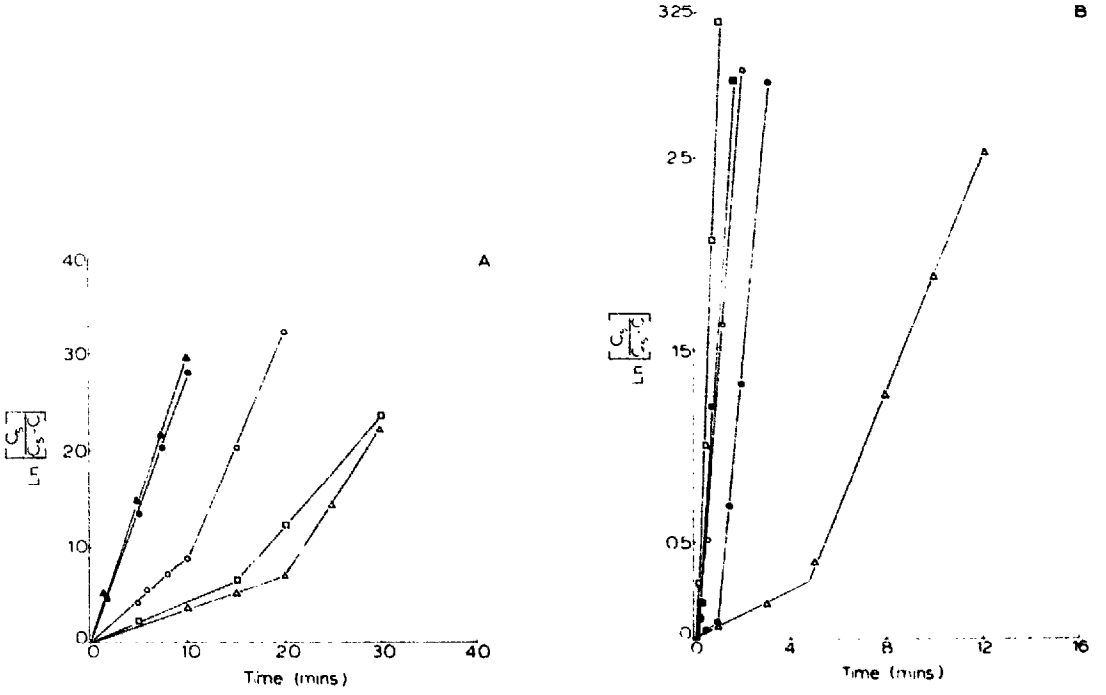

Fig. 4. A: $\ln\frac{C_s}{C_s - C}$ versus time plots to determine dissolution rates for oxytetracycline-lactose tablets of particle size fraction 20–30 μm compressed at 20 °C. △, M_1, $P_f = 0.757$; ○, M_1, $P_f = 0.799$; □, M_1, $P_f = 0.82$; ▲, M_2, $P_f = 0.757$; ●, M_2, $P_f = 0.821$. B: $\ln\frac{C_s}{C_s - C}$ versus time plots to determine dissolution rates for oxytetracycline-lactose tablets of particle size fraction 20–30 μm compressed at 20 °C. □, M_5, $P_f = 0.779$; ■, M_5, $P_f = 0.820$; △, M_5, $P_f = 0.885$; ○, M_6, $P_f = 0.806$; ●, M_6, $P_f = 0.893$.

TABLE 2

EFFECT OF PROPORTION OF LACTOSE ON VALUES OF DISSOLUTION RATE CONSTANTS FOR TABLETS AT PACKING FRACTION 0.82 COMPRESSED AND TESTED AT 20 °C

Sample code no.	% lactose	Particle size fraction (μm)	k_1	k_2
Physical mixtures				
M_1	25	0–10	0.166	0.055
		10–20	0.250	0.510
		20–30	0.426	1.12
M_2	50	0–10	1.15	*
		10–20	1.97	*
		20–30	27.1	*
M_3	75	0–10	0.24	0.75
		10–20	1.0	*
		20–30	14	*
Formulated mixtures				
M_4	25	0–10	0.320	0.76
		10–20	0.342	0.81
		20–30	0.368	2.60
M_5	50	0–10	0.875	3.14
		10–20	1.01	*
		20–30	15.7	*
M_6	75	0–10	0.413	1.50
		10–20	0.950	2.10
		20–30	12.6	*

* A single straight line with slope = k_1 was obtained.

slope k or two straight lines of slopes k_1 and k_2, depending on the packing fraction and the method of mixing, were obtained (Fig. 4A and B). The values of k_1 and k_2 for the 2 types of tablets containing 25–75% w/w lactose at $P_f = 0.82$ are listed in Table 2. The dissolution rates tended to maxima when the tablets contained 50% w/w lactose. They decreased with increasing particle size and the values for the formulated tablets were lower than those for the physically mixed tablets.

The rates at which water penetrated the tablets at a fixed P_f of 0.82 have been recorded in Table 1. It can be seen that the rate generally increased with increase in particle size and proportion of lactose but decreased with increase in compression temperature.

Discussion

The procedure for analyzing the results is laid out in Appendix 1. In the present work the calculations were carried out on a computer and the results are given in

TABLE 3

STATISTICAL SIGNIFICANCE OF RESULTS FOR TENSILE STRENGTH, DISINTEGRATION AND DISSOLUTION (t_{100}) TIMES OF TABLETS

Source of variation	Tensile strength ($MN \cdot m^{-2}$)			Disintegration time (min)			Dissolution time (min)			Rate of water penetration (cm/s) $\times 10^4$		
	Sum of squares	df	Variance ratio	Sum of squares	df	Variance ratio	Sum of squares	df	Variance ratio	Sum of squares	df	Variance ratio
Physically mixed tablets												
Particle size fraction D	6	2	500	324	2	2700	7154	2	5962	1367.3	2	170,875
Proportion of lactose P	7	2	583	174	2	1450	11,143	2	9286	163.2	2	20,375
Temperature U	23	2	1917	54	2	450	337	2	281	11.50	2	1500
D×U	0.20	4	8	26	4	108	126	4	53	3	4	188
D×P	0.62	4	26	234	4	976	8853	4	3688	140.8	4	8813
P×U	0.80	4	33.33	7	4	29	146	4	60	0.90	4	56
D×P×U	0.60	8	12.50	4	8	8	112	8	23	3.70	8	125
Residual	0.30	54		3	54		32	54		0.20	54	
Formulated tablets												
Particle size fraction D	9	2	56.25	6927	2	4330	32,855	2	3734	220.60	2	36,833
Proportion of lactose P	6	2	37.50	1513	2	946	78,272	2	8895	415	2	69,167
Temperature U	33	2	206.3	183	2	114	493	2	56	7.30	2	1167
D×U	0.70	4	2.20	36	4	11	63	4	4	0.20	4	14
D×P	1	4	3.00	326	4	102	21,217	4	1205	176.90	4	14,750
P×U	0.50	4	1.60	19	4	6	78	4	4	0.80	4	65
D×P×U	1	8	1.60	3	8	0.50	33	8	0.90	0.20	8	8
Residual	4.50	54		42	54		236	54		0.16	54	

Table 3. It can be seen from the values of the variance ratio that the individual effects of the variables on the tensile strengths, disintegration and dissolution times of both types of tablets were in the orders respectively of $U > P \approx D$; $D > P > U$; and $P > D \gg U$. The combined effects on tensile strength were in the orders of $P \times U > D \times P > D \times U$ for the physically mixed tablets and $D \times P > D \times U > P \times U$ for the formulated ones; for the disintegration and dissolution times of both types the order was $D \times P > D \times U \geqslant P \times U$.

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 as 2nd-order when it is influenced by the level of two others. In order to decide whether the interaction is significant one can either use a statistical analysis (Davies, 1954; Moroney, 1980) or use a graphical procedure. This is illustrated in Fig. 5a–c where the sums of the 3 tensile strengths from Table 4B have been plotted against the levels of D for different levels of P and U. The amounts by which the graphs depart from the horizontal are a measure of the extent to which the tensile strength depends on D. Their separation on the ordinate (in each subfigure) is a measure of the effect of P on tensile strength at each level of U, and the relative positions of the 3 graphs in Fig. 5A, B and C is a measure of the effect of U on tensile strength. From Fig. 5 and similar graphs, which for reasons of space are not shown, it was concluded that D, P

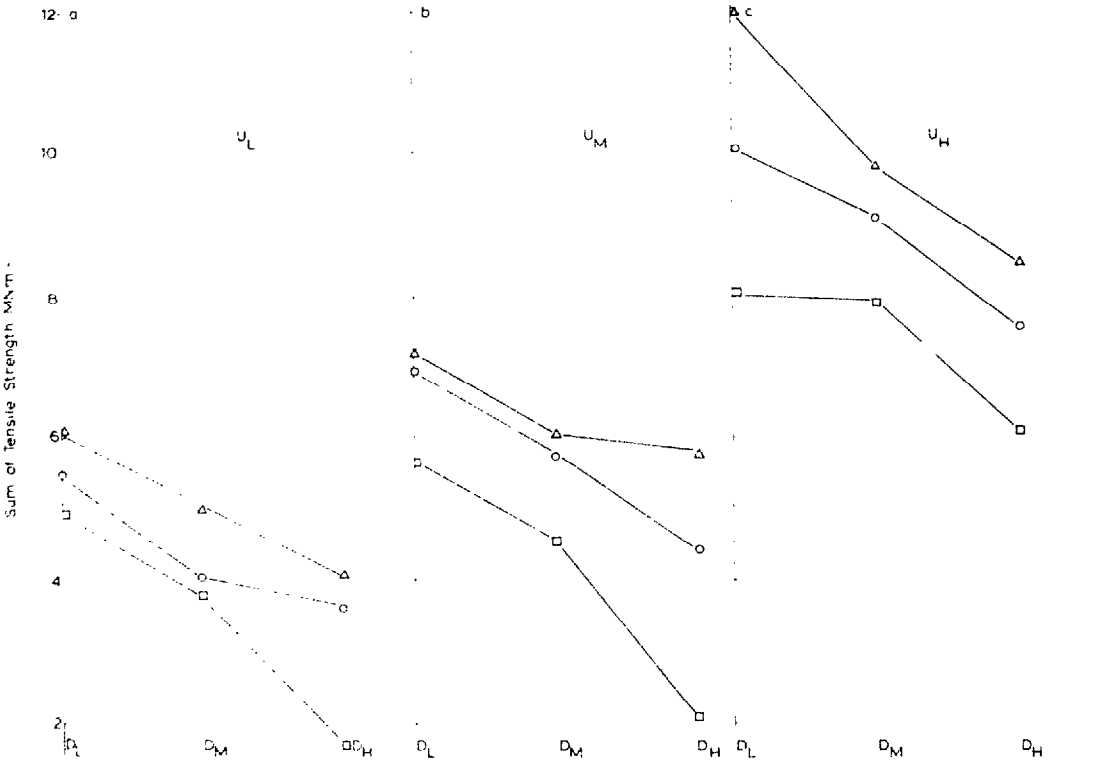

Fig. 5. Graphical representation of a second-order interaction between particle size (D), composition of mixture (P) and temperature (U) on the tensile strength of formulated oxytetracycline-lactose tablets at $P_f = 0.82$. △, P_L; ○, P_M; □, P_H.

and U had significant first-order and also significant second-order interactions in relation to the tensile strengths, disintegration and dissolution times of both the physically mixed and formulated tablets.

Considering first the effects of D, P and U on tensile strength, as D increases the tensile strength of the tablet decreases due to a reduction of the electrostatic, frictional and mechanical forces between the particles (Ashton et al., 1965; Walton and Pilpel, 1972). As for the effect of P, lactose is intrinsically less cohesive than oxytetracycline (Varthalis and Pilpel, 1976); hence its addition leads to the reduction in the tablets' tensile strength. Considering U, high temperatures combined with the high compression forces used in tableting and tensile testing have been shown to cause melting of asperities at very localized points of contact between particles leading subsequently to the formation of welded bonds (Jayasinghe et al., 1969; Pilpel and Britten, 1979). The strength of these predominates over all other forces acting between the particles (Kurup and Pilpel, 1979). Because more welded bonds are formed at high temperatures and pressures than at low ones, this explains why U has the biggest effect of all the variables on the tensile strengths of the tablets, whereas it was found in the previous investigation on the powders at lower pressures (Adeyemi and Pilpel, 1983) that D had the biggest effect.

Turning next to the disintegration and dissolution times, D has the biggest effect and increasing D reduces both times. This could be because of the increase in the size of capillary spaces between the particles which contribute to the transport of water through the tablets. Increasing P also reduces the disintegration and dissolution times and this is because lactose is water-soluble and makes the tablets hydrophilic. This is confirmed by the water penetration rates (Table 1). The increase in the rates with increasing D and P causes an increase in the pressure difference, ΔP_l which exists across the meniscus of the water entering each capillary of the tablet. This pressure difference is given by Carman (1941) as:

$$\Delta P_l = \frac{\gamma \cos \theta}{m} \tag{5}$$

where γ is the surface tension of water, θ is its contact angle at the capillary surface and m is the ratio of the cross-sectional area of the capillary and its perimeter. Obviously with the contact angle of water on lactose being less than 90° (Malamataris, 1981; Igwilo, 1982) ΔP_l will be high and penetration is fast. The increasing disintegration and dissolution times produced by increasing U is as expected since high temperatures and pressures during tableting produce welded bonds and therefore strong and impervious tablets.

It is apparent from this discussion that numerous mechanisms are involved in determining how alterations in the values of D, P and U affect the values of tensile strength, disintegration and dissolution (t_{100}) times. In some combinations the variables produce effects which are additive, in others they work in opposition. Thus in the physical mixtures the formation of welded bonds by heating could be counteracted by an increase in particle size or the percentage of lactose present, whereas in the formulated mixtures additional solid bonds would have been formed

during the processes of wet granulation and drying. Considerations such as these could explain some of the differences observed between the physically mixed and the formulated tablets and account generally for the findings reported about the different combinations of the variables (see opening of Discussion).

Appendix 1

Considering the tensile strength results at $P_f = 0.82$ from the formulated tablets, the replicate results for different combinations of D, P and U are set out in Table 4A. Summing the 3 replicates for each combination of the variables (as the first step for determining the variation between replicates) we obtain Table 4B.

TABLE 4A

TENSILE STRENGTHS IN TRIPLICATE FOR FORMULATED TABLETS AT $P_f = 0.82$

	Tensile strength ($MN \cdot m^{-2}$)								
	U_L			U_M			U_H		
	D_L	D_M	D_H	D_L	D_M	D_H	D_L	D_M	D_H
P_L	1.84	1.58	1.38	2.16	1.89	1.78	4.02	3.04	2.65
	1.93	1.60	1.39	2.44	1.94	1.88	3.79	3.30	2.71
	2.23	1.68	1.46	2.54	2.20	2.01	4.10	3.50	3.01
P_M	1.69	1.28	1.02	1.86	1.70	1.34	3.36	2.89	2.48
	1.82	1.43	1.22	2.40	1.94	1.50	3.45	3.04	2.61
	1.89	1.43	1.30	2.70	2.00	1.63	3.57	3.10	2.65
P_H	1.61	1.19	0.52	1.77	1.48	0.67	2.58	2.57	1.88
	1.64	1.25	0.55	1.90	1.50	0.72	2.71	2.61	2.00
	1.64	1.32	0.61	2.00	1.55	0.73	2.78	2.62	2.15

TABLE 4B

SUMMATION OF REPLICATE TENSILE STRENGTHS FROM TABLE 4A SUMS OF 3 TENSILE STRENGTHS ($MN \cdot m^{-2}$)

	U_L			U_M			U_H		
	D_L	D_M	D_H	D_L	D_M	D_H	D_L	D_M	D_H
P_L	6.0	4.86	4.23	7.14	6.03	5.67	11.91	9.84	8.37
P_M	5.40	4.14	3.54	6.90	5.64	4.47	10.38	9.03	7.74
P_H	4.89	3.75	1.68	5.67	4.53	2.12	8.07	7.80	6.03

We now group the tensile strength results into sets in which two of the variables are kept constant while the third is altered. Summing the values yields Table 4C (1), (2) and (3) in which each number represents the sum of 9 experimental values of tensile strength.

TABLE 4C

SUMS OF 9 TENSILE STRENGTHS ($MN \cdot m^{-2}$)

(1)

D_L			D_M			D_H		
P_L	P_M	P_H	P_L	P_M	P_H	P_L	P_M	P_H
25.05	22.50	18.63	20.73	18.81	16.08	18.27	15.75	9.83

(2)

U_L			U_M			U_H		
P_L	P_M	P_H	P_L	P_M	P_H	P_L	P_M	P_H
15.09	13.08	10.32	18.84	17.01	12.32	30.12	27.15	21.90

(3)

U_L			U_M			U_H		
D_L	D_M	D_H	D_L	D_M	D_H	D_L	D_M	D_H
16.29	12.75	9.45	19.71	16.20	12.26	30.36	26.67	22.14

We now add together all the numbers from Table 4C (1), (2) or (3) which have a common level of each of the three variables D, P and U and obtain Table 4D. In this, each number now represents the sum of 27 results out of the total of the 81 measurements made of tensile strengths as shown in Table 4A.

TABLE 4D

SUMS OF 27 TENSILE STRENGTH VALUES ($MN \cdot m^{-2}$)

(1)	D_L	D_M	D_H
	66.36	55.62	43.85
Grand Total (G) = 166			
(2)	P_L	P_M	P_H
	64.05	57.24	44.54
Grand Total (G) = 166			
(3)	U_L	U_M	U_H
	38.49	48.17	79.17
Grand Total (G) = 166			

The correction factor (CF) is defined as:

$$CF = \frac{G^2}{N}$$

where N is the total number of measurements and G is their numerical sum for each variable.

In this example, $CF = (166)^2/81 = 340$

We can now do the analysis of variance for the effect of each variable, first separately, then two at a time and then three at a time. This is done by calculating sums of squares, degrees of freedom (df), variance estimates and variance ratios as follows.

(1) Sums of squares and df of one variable

Taking D as the variable the tensile strength values in Table 4D (1) are squared, their sum is divided by the number of measurements involved, i.e. 27 and the correction factor is subtracted; thus

$$\tfrac{1}{27}[66.40^2 + 55.60^2 + 43.90^2] - 340 = 9.0$$

Since three levels of D have been employed, the number of degrees of freedom, df = 2. A similar procedure is adopted for P and U as the variables using Tables 4D (2) and (3), respectively.

(2) Sums of squares and df of two interacting variables

Taking D and P as the two variables, the tensile strengths in Table 4C (1) are squared and their sum is divided by the number of measurements involved, i.e. 9. Subtracting the CF and the sum of squares of each variable (calculated as in (1) above) gives:

$$\tfrac{1}{9}[25.05^2 + 22.50^2 + 18.63^2 + 20.73^2 + 18.81^2 + 16.08^2 + 18.27^2 + 15.75^2 + 19.83^2]$$

$$-[9.00 + 6.00 + 340] = 1.00$$

The df for the interaction is now $2 \times 2 = 4$

A similar procedure, mutatis mutandis, is adopted for the other pairs of variables.

(3) Sum of squares and df for three interacting variables

Each tensile strength value in Table 4B is squared and their sum divided by the number of replicates, i.e. 3. Subtracting the CF, the sums of squares of each variable (calculated as in (1) above) and of the pairs of variables (calculated as in (2) above) gives:

$$\tfrac{1}{3}[6.0^2 + 4.86^2 + 4.23^2 + 7.14^2 + 6.03^2 + \ldots + 8.07^2 + 7.8^2 + 6.03^2]$$

$$-[9.00 + 6.00 + 33 + 1.0 + 0.70 + 0.50 + 340] = 1.00$$

The df for this interaction is now $2 \times 2 \times 2 = 8$

(4) The total sum of squares is obtained by summing the squares of all the tensile strengths in Table 4A and subtracting the CF thus:

$$[1.80^2 + 1.60^2 + 1.40^2 + 2.20^2 + \ldots + 0.70^2 + 2.80^2 + 2.60^2 + 2.20^2] - 340 = 55.70$$

Since total number of measurements performed was N (= 81), the number of degrees of freedom, df = N − 1 = 80.

(5) The residual sum of squares is obtained by subtracting a he sums of squares from (1), (2) and (3) above from the total sum of squares in (4 ius:

$[55.70 - 51.20] = 4.5$

(6) The residual df is obtained by subtracting the sum of all the dfs from (1) to (3) from the total df, i.e.:

$80 - (2 \times 3 + 4 \times 3 + 8) = 54$

(7) The variance estimate is obtained by dividing each sum of squares by its appropriate df. In the example shown in (1) above, the variance estimate is

$9.0/2 = 4.5$

(8) The residual variance estimate is obtained by dividing the residual sum of squares by the residual df, i.e.:

$4.5/54 = 0.08$

(9) The variance ratio F, is obtained by dividing each variance estimate by the residual variance estimate and its value in the above example is:

$4.5/0.08 = 56$

The magnitude of the variance ratio provides a measure of the effect that the variables or the variables in combination have had on the measured properties of the tablets.

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