CHAPTER 4

THE STATISTICAL ANALYSIS OF THE RESULTS DERIVED FROM PARACETAMOL TABLETS.

4.1. Introduction.

This chapter describes the results of the analysis of variance (ANOVA) of treatments involved in a complete factorial experiment. It covers only the experiment involving paracetamol. The analyses are discussed in sections dealing with weight variation, porosity, tensile fracture stress, friability, liquid uptake as determined by gamma scintigraphy and dissolution. A summary of the effects of the treatments rather than the determinants is also included.

The term ´treatment´ is used in the following discussion to describe the experimental variable under consideration, e.g. the treatment ´mixing time´ is the change from 1 minute mixing to 5 minutes mixing. The subsidiary (suffixed) tables show the magnitude of the effect (e.g. T90% in minutes) attributable to a treatment or interaction derived from the complete factorial experiment. That is, the sum of the effects of a given level of a treatment, (or levels of different treatments) divided by the number of effects included. A determinant is the experimental factor analysed, e.g. the tensile fracture stress. Table 4.1 gives an explanation of the terms used in the analysis of variance (ANOVA) tables.

It should be noted that where a significant interaction between treatments exists the mean effect attributable to either of the single treatments must be considered as part of the interaction rather than as an isolated treatment.

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Table 4.1
The terms used in the ANOVA tables.

SINGLE TREATMENTS.

MIXTIME - The treatment of altering the mixing time

STARCH - The treatment of altering the starch concentration

SIZE - The treatment of altering the drug particle size.

PRESSURE - The treatment of altering the compaction pressure.

INTERACTIONS.

MIXTIME.STARCH - The interaction between mixing time and starch concentration,

and similarly for the other two, three or four factor interactions thus;

A.B.C - The interaction between A, B and C.

GRAND MEAN - The mean of all the experimental values considered in the analysis of variance.

RESIDUAL - That part of the sum of squares not accounted for by the treatments, an expression of the variability of all the data considered.

continued

Table 4.1 (continued)

COLUMN EXPLANATION.

SOURCE OF VARIATION	The treatment(s) under consideration. The data relating to the source of variation being used to derive the other columns in the row.
DEGREES OF FREEDOM	A measure of the number of independent values which contribute to the derived statistics. A more detailed explanation may be found in Davies (1976).
SUM OF SQUARES %	The sum of squares expressed as a percentage of the total. The sum of squares being the sum of the square of the difference between a value and the mean of the group of values.
MEAN SQUARES	The sum of squares divided by the degrees of freedom.
VARIANCE RATIO	The mean square of a treatment or interaction divided by the residual mean square.
SIGNIFICANCE	The probability of obtaining an effect as extreme as that attributable to a treatment under the null hypothesis that there was no effect,(´F´ test).

4.2 Statistical Analysis of the Treatments Relating to the Tablet Weight Variation of Paracetamol Tablets.

The analysis of variance (ANOVA) based on the coefficient of tablet weight variation is shown in Table 4.2. Two treatments (mixtime and size) and one interaction (mixtime.size) were significant, that is, the variance ratio was sufficiently high to indicate that the source of variation had a real effect. The probability that this effect was greater than that expected under the null hypothesis, (that the effect was accounted for by the variation in the original data), is given by the significance level, taken from the ´F´ distribution in statistical tables (Fisher and Yates, 1947). The subsidiary tables (Tables 4.2a-c) show the mean coefficient of weight variation attributable to the individual levels of a treatment derived from the sum of those batches made with that level of the treatment, divided by the number of batches involved. Thus, for the treatment ´mixtime´ 12 batches were involved at each level (1 or 5 min).

The most significant treatment affecting the coefficient of weight variation of the paracetamol tablets was the drug particle size. The mean coefficients attributable to the different size fractions are shown in Table 4.2a. Table 4.2b shows the effect attributable to the mixing time, and Table 4.2c the effect of the interaction between mixing time and drug particle size. The figures in Tables 4.2a and 4.2b can be simply derived from the interaction shown in Table 4.2c.

TABLE 4.2

ANOVA table based on the coefficient of weight variation of paracetamol tablets.

$SS = \frac{MS \times DF}{\text{[illegible]}}$ $= \frac{MS}{RMS}$

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	8.55	19.58	40.32 **
STARCH	1	0.07	0.16	0.33
SIZE	1	55.97	128.18	263.96 ***
PRESSURE	2	2.37	2.72	5.60
MIXTIME.STARCH	1	0.45	1.03	2.13
MIXTIME.SIZE	1	10.48	24.01	49.45 **
STARCH.SIZE	1	0.02	0.04	0.09
MIXTIME.PRESSURE	2	8.17	9.35	19.26
STARCH.PRESSURE	2	0.27	0.31	0.63
SIZE.PRESSURE	2	3.13	3.58	7.38
MIXTIME.STARCH.SIZE	1	0.53	1.22	2.51
MIXTIME.STARCH.PRESSURE	2	0.50	0.57	1.17
MIXTIME.SIZE.PRESSURE	2	8.65	9.91	20.41
STARCH.SIZE.PRESSURE	2	0.41	0.47	0.98
RESIDUAL	2	0.42	0.49	
TOTAL	23	100.00 99.99	9.96	

GRAND MEAN 3.54 %

TOTAL NUMBER OF OBSERVATIONS 24

SIGNIFICANCE LEVEL *** >99% , ** >97.5%

continued

Table 4.2a.

The mean coefficient of tablet weight variation (%) attributable to the drug particle size.

		drug particle size (μm)	
		-20	+20
coefficient of weight variation	(%)	5.85	1.23

Table 4.2b.

The mean coefficient of tablet weight variation (%) attributable to the mixing time.

		mixing time (min)	
		1	5
coefficient of weight variation	(%)	4.44	2.64

Table 4.2c.

The mean coefficient of tablet weight variation (%) attributable to the interaction between the mixing time and the drug particle size.

		mixing time (min)	
		1	5
drug particle size (μm)	-20	7.75	3.95
	+20	1.13	1.33

The coefficient of weight variation was significantly reduced by increasing the drug particle size (Tables 4.2 and 4.2a), indicating that the powder flow was much more consistent with the larger drug size. Paracetamol is known to be a highly electrostatic drug i.e. having a high surface charge, (Gold and Palermo 1965). With smaller particles the effect of electrostatic bonding would be greater than with larger particles, the larger particles having a lower surface/mass ratio and the inertia to overcome any electrostatic bonds formed during movement. The specific surface area of the larger particles is also less than that of smaller particles, so that for the same formula, less surface is available to form temporary bonds. This was probably manifest both in the delivery of the powder to the die and in the die itself.

An increase in the mixing time reduced the mean attributable coefficient of weight variation, (Table 4.2b). The effect of a longer mixing time is to increase the intermingling of the discrete components of a powder up to the point where this is balanced by the segregation of the components. The preliminary experiments described in Chapter 2 suggested that the mixing times chosen could reasonably be taken as ´partially mixed´ (1 min) and ´completely mixed´ (5 min), the latter representing a state of balance between mixing and segregation. In these formulations the most important effect of the longer mixing time was probably the distribution of the magnesium stearate and the Aerosil, which undergo ´ordered´ mixing in that they tend to spread over or coat any more stable surfaces present, (Lerk and Bolhuis 1977, Bolhuis et al. 1975).

Magnesium stearate was included in the formulations as a lubricant, but a surface coating of this substance has also been shown to reduce surface electrostatic charge (Gold and Palermo 1965). An increased distribution of the magnesium stearate as a result of a longer mixing time might therefore be expected to reduce both electrostatic and mechanical particle interactions. Table 4.2b shows the reduction in the coefficient of weight variation which may be attributed to the more consistent powder flow as a result of the distribution of magnesium stearate with a longer mixing time.

The interaction shown in Table 4.2c gives a more detailed description of the effects of altering the mixing time and the drug particle size. This table gives an indication of the relative importance of the two treatments to the coefficient of tablet weight variation. A change in the drug particle size influences the weight variation to a much greater extent than a change in the mixing time. Table 4.2c also serves to illustrate the value of this type of experimental design in that the effect of altering the mixing time can be seen to be relevant only with the smaller drug particles. This type of interaction being easily overlooked in isolated experiments on either the particle size or the mixing time. The interaction indicates that the distribution of magnesium stearate had a considerable effect when electrostatic bonding was a major factor but little effect when the surface charge/mass ratio was reduced.

4.3 Statistical Analysis of the Treatments Relating to the Porosity of Paracetamol Tablets.

The ANOVA using tablet porosity as the determinant is shown in Table 4.3. The use of the tablet density or relative density as the determinant produces identical tables to that for porosity as they are related to the porosity by Equations 2.4 and 2.5. The residual mean square derived from the four factor interaction was insufficient to indicate which treatments were significant, i.e. there was very little experimental variation, therefore a residual mean square was derived from the 3 and 4 factor interactions, the assumption being that there were no significant 3 factor interactions. As the total residual sum of squares of the four 3 factor interactions plus the single 4 factor interaction comprised only 2.15% of the total sum of squares this assumption was considered as being reasonable. It should be noted that the range of porosities attributable to all but the compaction pressure was only about 1% (Tables 4.3b-e). Therefore, although the effects of some of the treatments were statistically significant, the effects should be interpreted with respect to their practical application.

The most significant treatment affecting the porosity was the compaction pressure. Table 4.3a shows that the mean attributable porosity decreased with an increase in compaction pressure. This implies that closer particle-to-particle proximity was achieved on increasing the compaction pressure which was not lost on ejection of the tablet from the die, that is, an overall increase in bonding took place.

TABLE 4.3

ANOVA table based on the Porosity of paracetamol tablets.

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	6.15	4.29	25.75 ****
STARCH	1	8.08	5.63	33.81 ****
SIZE	1	6.94	4.84	29.05 ****
PRESSURE	2	64.22	22.37	134.40 ****
MIXTIME.STARCH	1	1.02	0.71	4.28
MIXTIME.SIZE	1	3.85	2.68	16.11 ***
STARCH.SIZE	1	1.82	1.27	7.60 **
MIXTIME.PRESSURE	2	1.88	0.66	3.94
STARCH.PRESSURE	2	2.17	0.76	4.54
SIZE.PRESSURE	2	1.72	0.60	3.60
RESIDUAL	9	2.15	0.17	
TOTAL	23	100.00	3.03	

GRAND MEAN 14.33 %

TOTAL NUMBER OF OBSERVATIONS 24

SIGNIFICANCE LEVEL **** >99.9%, *** >99% , ** >97.5%

continued

Table 4.3a.

The mean tablet porosity attributable to the compaction pressure.

	compaction pressure (MNm^{-2})		
	100	150	200
porosity (%)	16.19	13.88	12.94

Table 4.3b.

The mean tablet porosity attributable to the starch concentration.

	starch concentration (%)	
	1	7
porosity (%)	13.85	14.82

Table 4.3c.

The mean tablet porosity attributable to the drug particle size.

	drug particle size (μm)	
	-20	+20
porosity (%)	14.78	13.89

continued

Table 4.3d.

The mean tablet porosity attributable to the mixing time.

	mixing time (min)	
	1	5
porosity (%)	13.91	14.76

Table 4.3e.

The mean tablet porosity (%) attributable to the interaction between the mixing time and the drug particle size.

		mixing time (min)	
		1	5
drug particle size (μm)	-20	14.69	14.87
	+20	13.12	14.64

The effects of altering the mixing time, the starch concentration or the drug particle size were all significant at about the same probability, (Table 4.3).

Increasing the starch concentration increased the tablet porosity (Table 4.3b) probably by one or both of two methods. The starch grains had a greater mean surface volume diameter (Table 3.2) than the Avicel it replaced in the formulations with the higher starch concentration. This may have reduced the packing efficiency of the particles on filling the die and in the initial stages of compaction, leaving more void spaces after compaction. A greater influence was probably exerted by the differences in response to compaction of the starch and the Avicel, the Avicel exhibiting less elastic recovery than starch (Jones 1979). This meant that at the higher starch concentrations, although the same porosity may have been reached under imposed stresses as the lower starch level, there would be a greater degree of elastic recovery of the particles when the stresses are removed. As the surrounding Avicel matrix will have been plastically deformed, (David and Augsberger 1977), the stresses induced by elastic recovery of the starch grains disrupts the tablet matrix increasing the number of void spaces. This would be expected to reduce the tablet strength.

Table 4.4c p 161 true

Increasing the mixing time resulted in an increase in the mean attributable tablet porosity (Table 4.3d). This is slightly surprising as the greater distribution of lubricant might be expected to improve particle flow and hence result in an improved packing arrangment leading to an increase in possible bonding sites on compaction. An examination of Tables 4.2 and 4.2b, confirms that there was a significant reduction in the coefficient of weight variation with a longer mixing time, i.e. more consistent die filling. The greater porosity with a longer mixing time may therefore have been due to the reduction in permanent bonds formed due to the presence of interparticulate magnesium stearate. This would allow any elastic recovery to take place against a reduced number of constraining bonds as well as reducing the overall number of bonds formed.

A significant decrease in the mean attributable porosity was produced by increasing the drug particle size, (Tables 4.3 and 4.3c). This may have been due to a closer initial packing state. The less consistent flow of the smaller drug fraction, (Table 4.2a), would result in a much more open initial packing state supported by electrostatic bridging between particles. On compaction these would break down but continue to reform and resist the compaction stresses imposed. Thus the final compact will contain void spaces where electrostatic or other bonding has taken place before the optimum i.e. closest, particle rearrangment has been achieved. This process may be visualised by reference to the interlocking stones above an arch. If the stones bond together they can form a structure which will resist stresses above it and enclose an empty space. If the stones do not hold together the structure will collapse under imposed stress leaving very little empty space. The more consistent flow with the larger drug particle size tends to suggest that a closer initial packing state may be achieved.

The interaction between mixing time and drug particle size was significant (Table 4.3), the mean porosities attributable to the interaction being presented in

Table 4.3e. This shows that the porosity of the combination of a longer mixing time and a smaller drug particle size was not significantly greater than the small drug size, short mixing time, or the large drug size, longer mixing time combinations. From the consideration of the individual factors, an increase in the mixing time or a reduction in the drug particle size resulted in a higher porosity, therefore the highest porosity might be expected from the combination of small size and long mixing time. The explanation probably lies in the action of magnesium stearate, which besides interfering in interparticulate bonding also acts as a lubricant and reduces electrostatic charges, (Gold and Palermo, 1965). The lubricant and charge reduction properties of the magnesium stearate will have a greater effect where electrostatic forces are more pronounced, that is, with the smaller size drug fraction. A combination of small drug particle size and a long mixing time might therefore be expected to flow more consistently than the combination of a small particle size and a short mixing time, (Table 4.2c). This should increase the initial packing efficiency and hence reduce the porosity. However, the reduction in bond strength from the interparticulate lubricant simultaneously allows a greater degree of elastic recovery, i.e. increased porosity. Thus, the overall effect with this combination will be a lower porosity than expected from a consideration of the effects of mixing time or drug particle size in isolation. This again illustrates the value of a designed experiment. A simple experiment on the effect of mixing time on porosity followed by one on drug particle size would not show that the mode of action of either of these factors is influenced by the other.

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4.4. Statistical Analysis of the Treatments Relating to the Tensile Fracture Stress of Paracetamol Tablets.

The most significant effect on the tensile fracture stress was attributable to altering the mixing time (Table 4.4). The subsidiary table (4.4a) shows that the mean attributable tensile fracture stress decreased with an increase in mixing time. This was most probably due to the formation of a film of magnesium stearate around the particles, which interfered with bond formation between particles on compaction, thus decreasing the overall compact strength. This phenomenon has been explored by Bolhuis et al. (1975), Ganderton (1969) and others. The decrease in tensile fracture stress implies that the principal bonding was not due to brittle fracture, if it were, then no decrease in strength would be expected, (Bolhuis et al. 1975). This does not necessarily mean that no particle fracture took place during compaction.

The second most significant treatment (Table 4.4) was the drug particle size. Table 4.4b shows that increasing the drug particle size decreased the mean attributable tensile fracture stress. A smaller particle size will have a greater specific surface area. Therefore more surface is available for bonding to take place and the magnesium stearate will be distributed over a larger area. Both actions contributing to a greater degree of bonding between particles when smaller drug particles were used compared to larger particles.

TABLE 4.4.

ANOVA table based on the tensile fracture stress of paracetamol tablets.

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	57.19	1.5442	870.57 ***
STARCH	1	9.91	0.2677	150.91 ***
SIZE	1	19.58	0.5287	298.07 ***
PRESSURE	2	10.73	0.1448	81.65 **
MIXTIME.STARCH	1	0.11	0.0030	1.69
MIXTIME.SIZE	1	0.24	0.0065	3.66
STARCH.SIZE	1	0.12	0.0032	1.80
MIXTIME.PRESSURE	2	0.11	0.0015	0.82
STARCH.PRESSURE	2	0.02	0.0002	0.13
SIZE.PRESSURE	2	1.18	0.0160	9.00
MIXTIME.STARCH.SIZE	1	0.41	0.0111	6.23
MIXTIME.STARCH.PRESSURE	2	0.13	0.0017	0.96
MIXTIME.SIZE.PRESSURE	2	0.04	0.0006	0.34
STARCH.SIZE.PRESSURE	2	0.10	0.0013	0.73
RESIDUAL	2	0.13	0.0018	
TOTAL	23	100.00	0.1174	

GRAND MEAN 0.8222 MNm^{-2}

TOTAL NUMBER OF OBSERVATIONS 24

SIGNIFICANCE LEVEL *** >99% , ** >97.5%

continued

Table 4.4a.

The mean tensile fracture stress attributable to the mixing time.

	mixing time (min)	
	1	5
tensile fracture stress (MNm^{-2})	1.076	0.569

Table 4.4b.

The mean tensile fracture stress attributable to the drug particle size.

	drug particle size (μ)	
	-20	+20
tensile fracture stress (MNm^{-2})	0.971	0.674

Table 4.4c.

The mean tensile fracture stress attributable to the starch concentration.

	starch concentration (%)	
	1	7
tensile fracture stress (MNm^{-2})	0.928	0.717

continued

Table 4.4d.

The mean tensile fracture stress attributable to the compaction pressure.

	compaction pressure (MNm^{-2})		
	100	150	200
tensile fracture stress (MNm^{-2})	0.675	0.852	0.940

Table 4.4e.

The mean tensile fracture stress (MNm^{-2}) attributable to the interaction between the drug particle size, the mixing time and the compaction pressure.

		drug particle size (μm)			
		-20		+20	
mixing time (min)		1	5	1	5
compaction pressure (MNm^{-2})	100	1.044	0.527	0.796	0.334
	150	1.245	0.732	0.952	0.477
	200	1.433	0.842	0.985	0.499

These effects probably accounted for the major part of the decrease in tensile fracture stress when the drug particle size was increased. However, there exists the possibility of a change in crystal characteristics with size; the larger the crystal, the less able it might be to resist imposed stresses. This change may be due to the pre-processing of the drug e.g. during classification or milling during manufacturing. These processes impose stresses on the larger size input material which may break it down to a smaller sized output material. The smaller fraction of the output will have dissipated these stresses by fracture. The larger fraction of the output material may have absorbed the imposed stresses, but not dissipated them as completely as the smaller fraction. The larger fraction might therefore be in a pre-strained condition, probably as a crystal with incipient flaws. These could provide a focus for crystal fracture when further stress is imposed, particularly tensile rather than compressive stress such as in a diametral compression test. The only way of exploring this would be by stressing individual crystals of the different size fractions. This may be similar to the rapid increase in tensile fracture stress of silicon and zinc oxide whiskers as the diameter decreases below 15 micrometers described by Gordon (1976).

The effect of altering the starch concentration (Table 4.4c) may be explained using the same arguments as for the effect of changing the drug particle size. The mean surface volume diameter of starch was greater than that of the Avicel it replaced in the formulation, (Table 3.2). The formulations containing the higher concentrations of starch will therefore have a smaller total surface area than the corresponding low starch concentration formulations. The quantity of magnesium stearate between particles in the high starch concentration tablets will therefore be greater, with a correspondingly greater probability of poor bond formation and thus a lower tensile fracture stress. The total surface area available for bonding would also be reduced.

Jones (1979) presented stress relaxation profiles for Avicel and starch taken from the Avicel Application Bulletin (not dated), which indicated that the elastic recovery of starch was greater than that of Avicel. This may play a significant role in the reduction of the tensile fracture stress. The greater elastic recovery of the starch compared to the Avicel may be sufficient to break some of the bonds formed during plastic deformation at the peak compaction force. The higher the starch concentration, the greater the number of bonds broken and the weaker the tablet. This hypothesis may be supported by the increase in mean tablet porosity attributable to the higher starch concentration, (Table 4.3b), where the elastic recovery of the starch leaves void spaces as it returns from its position at maximum deformation. The reduction in tensile fracture stress may therefore have been due, under this mechanism, to a reduction in the number of bonds or bond strengths caused by the elastic recovery or by the increase in tablet defects (void spaces) with the increased starch concentration. The small disruptions caused by the elastic recovery of starch grains providing the focus for the initiation of fracture.

The tensile fracture stress increased as the compaction pressure was raised (Tables 4.4 and 4.4d). This was due to an overall increase in particle-to-particle proximity with a greater probability of bond formation. It was however interesting to note that this increase with compaction pressure was not linear, particularly in those batches where the other treatments, e.g. mixing time, had a pronounced effect, (Table 3.9). p106

size.

The individual treatments may be explained in terms of the mechanical properties of the formulations involved but the relative significance of the treatments is also of interest. In this study the order of significance was mixing time > drug particle size > starch concentration > compaction pressure. This order reflected the magnitude of the mean effect attributable to the change in level of a factor, that is for example, the change from a mixing time of 1 to 5 minutes was greater than increasing the compaction pressure from 100 to 200MNm^{-2} .

Thus with these formulations the effect of over mixing would not be recoverable by increasing the compaction pressure. Increasing the starch concentration also had a greater effect than increasing the compaction pressure by 50MNm^{-2} , and the effect of altering the drug particle size was greater than doubling the compaction pressure. The reduction in tensile fracture stress due to overmixing may therefore be minimised by using less starch and a small drug size at a high compaction pressure. The absence of significant interactions (Table 4.4) indicates that the treatments were operating independently and the resulting tensile fracture stress of a combination of treatments was additive.

4.5. Statistical Analysis of the Treatments Relating to the Friability of Paracetamol Tablets.

The analysis of variance relating to the friability showed no highly significant treatments (Table 4.5). This indicates that the residual estimate based on the four factor interaction was itself significant i.e. that the individual batch sum of squares were significantly different. The experimental coefficient of variation of 68% confirms this. The situation probably arose due to the nature of the friability test itself, which although involving relatively large numbers of tablets, did not form an adequate representation of a given batch. The breakage of tablets into large pieces would seem to be the source of the discrepancy, introducing disproportionate weight losses and therefore high friabilities. The conclusion must be that this test may only be useful where no tablet breakage occurs. Having said that, an inspection of Table 3.7 does produce some qualitative information. A comparison of batches 10, 11 and 12 with batches 22, 23 and 24 respectively, showed a marked decrease in friability. The only difference between these groups was the drug particle size, the smaller drug size fraction having the lower friability. It may also be noted that the tensile fracture stress in batches 10-12 became less dependent on the compaction pressure, at higher compaction pressures. This may be confirmed by examining the correlation coefficient between tensile fracture stress and compaction pressure, which were 0.833, 0.473 and 0.072 for pressures of 103, 157 and 198MNm^{-2} respectively (Table 3.9). This tends to

TABLE 4.5.

ANOVA table based on the Friability of paracetamol tablets

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	16.88	263.81	27.95
STARCH	1	12.15	189.87	20.12
SIZE	1	6.59	103.07	10.92
PRESSURE	2	8.55	66.80	7.08
MIXTIME.STARCH	1	9.77	152.69	16.18
MIXTIME.SIZE	1	8.87	138.65	14.69
STARCH.SIZE	1	5.75	89.92	9.53
MIXTIME.PRESSURE	2	8.50	66.42	7.04
STARCH.PRESSURE	2	4.37	34.13	3.62
SIZE.PRESSURE	2	2.68	20.95	2.22
MIXTIME.STARCH.SIZE	1	6.52	102.00	10.81
MIXTIME.STARCH.PRESSURE	2	4.54	35.49	3.76
MIXTIME.SIZE.PRESSURE	2	2.09	16.35	1.73
STARCH.SIZE.PRESSURE	2	1.54	12.04	1.28
RESIDUAL	2	1.21	9.44	
TOTAL	23	100.00	67.97	

GRAND MEAN 4.51%

TOTAL NUMBER OF OBSERVATIONS 24

NO SIGNIFICANT TREATMENTS

suggest that the higher pressure was near the lamination point despite the tablets apparently failing in tension, (Section 2.5.3). (p69) p70

4.6. Statistical Analysis of the Treatments Relating to the Uptake of Liquid by Paracetamol Tablets.

The time for 50% liquid uptake represents ed a measure of the rate of liquid ingress into a tablet. This was is a combination of the rate of penetration and the rate of saturation of the matrix. The figure is a fraction of the plateau level representing total saturation and was determined under different conditions to the drug dissolution test. It was calculated on the basis of volume so that 50% uptake does not mean that the solvent front had progressed half way along the tablet radius, nor does it mean that 50% of the tablet volume had reached saturation. It indicates only that 50% of the liquid required for saturation had passed the outside edge of the tablet. To distinguish this figure from the time for 50% of the drug to appear in solution (T50%), it will be refered to as the median liquid uptake (M50%).

It is interesting to note the difference in time scale between the M50% (0.5 4 to 3.5 6 min) and the T50% (2 .2 to 17.5 min, Table 3.7). Those batches manufactured with low mixing times and high starch concentrations (batches 7-9 and 19-21, Table 3.4), showed the least difference, particularly if the time for transport to the spectrophotometer (1 min) is taken away from the T50%. With these batches the M50% times (27-88 sec)

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are about one third of the times for 50% drug release (72-228 sec). This suggests that the penetration rate may have had a strong influence on the dissolution process with these batches.

The most significant treatment affecting the liquid uptake was the mixing time (Table 4.6). The mean attributable time for 50% uptake (M50%) increased with an increase in mixing time (Table 4.6a). This was probably the result of the increased distribution of magnesium stearate rendering a greater number of surfaces hydrophobic.

The mean M50% attributable to different drug particle sizes are presented in Table 4.6b. This shows that an increase in the drug particle size significantly increased the time for 50% liquid penetration. Liquid uptake probably took place through the microcrystalline cellulose structure as a result of the breakage of hydrogen bonds on hydration, (Reier and Shangraw 1966). This would have been inhibited by the presence of magnesium stearate at the particle interfaces (hence the significant effect of mixing time) or by meeting other hydrophobic surfaces, i.e. drug particles (Table 1.4). The more rapid liquid penetration (shorter M50%) with the smaller drug particle size may have been due to the distribution of relatively hydrophobic surfaces in the tablet matrix, the larger drug particles presenting larger continuous areas resistant to wetting. This would extend the liquid path necessary to bypass the larger particles as illustrated in Figure 4.1.

See also p18 & 23

169, 200

p20

TABLE 4.6.

ANOVA table based on the liquid uptake into paracetamol tablets.

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO	
MIXTIME	1	53.30	43902.49	1187.53	****
STARCH	1	0.06	49.61	1.34	
SIZE	1	14.52	11957.60	323.45	***
PRESSURE	2	13.45	5537.62	149.79	***
MIXTIME.STARCH	1	0.06	48.63	1.32	
MIXTIME.SIZE	1	5.60	4616.49	124.87	***
STARCH.SIZE	1	1.42	1168.07	31.60	
MIXTIME.PRESSURE	2	2.86	1176.80	31.83	
STARCH.PRESSURE	2	0.60	248.86	6.73	
SIZE.PRESSURE	2	0.39	162.51	4.40	
MIXTIME.STARCH.SIZE	1	0.74	612.52	16.57	
MIXTIME.STARCH.PRESSURE	2	0.43	178.08	4.82	
MIXTIME.SIZE.PRESSURE	2	6.34	2609.56	70.59	**
STARCH.SIZE.PRESSURE	2	0.14	58.01	1.57	
RESIDUAL	2	0.09	36.97		
TOTAL	23	100.00	3581.40		

GRAND MEAN 97.8 s

TOTAL NUMBER OF OBSERVATIONS 24

SIGNIFICANCE LEVEL **** >99.9%, *** >99% , ** >97.5%

continued

Table 4.6a.
The mean liquid uptake attributable to the mixing time.

	mixing time (min)	
	1	5
liquid uptake (s)	55.0	140.5

Table 4.6b.
The mean liquid uptake attributable to the drug particle size.

	drug particle size (μm)	
	-20	+20
liquid uptake (s)	75.4	120.1

Table 4.6c.
The mean liquid uptake attributable to the compaction pressure.

	compaction pressure (MNm^{-2})		
	100	150	200
liquid uptake (s)	70.3	100.3	122.7

continued

Table 4.6d.

The mean liquid uptake (s) attributable to the interaction between mixing time and drug particle size.

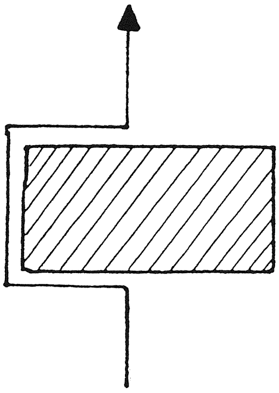
		mixing time (min)	
		1	5
drug particle size (μm)	-20	46.5	104.3
	+20	63.4	176.7

Table 4.6e.

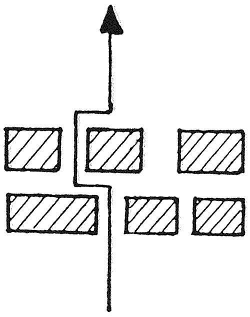
The mean liquid uptake (s) attributable to the interaction between drug particle size, mixing time and compaction pressure.

		drug particle size (μm)			
		-20		+20	
mixing time (min)		1	5	1	5
compaction pressure (MNm^{-2})	100	34.6	70.0	37.6	138.9
	150	66.3	80.3	59.3	195.2
	200	38.7	162.7	93.4	196.0

Number ratio 1:20   Surface ratio 1:2·5



Large hydrophobic inclusion leading to a long path length deviation for penetrating liquid



Small hydrophobic inclusions leading to much shorter path length deviation for penetrating liquid

Figure 4.1

The influence of hydrophobic inclusions on the penetration of liquid into a hydrophilic tablet matrix.

The higher porosity associated with the smaller drug particle size (Table 4.3c) might have been expected to provide additional routes to enhance liquid penetration. However a higher starch concentration also significantly increased the porosity (Table 4.3b) but did not significantly affect the M50%, (Table 4.6).

ie can't just be porosity

One of the mechanisms proposed to account for the action of starch as a disintegrant is its ability to provide channels for liquid uptake, (Table 1.5). The lack of significant effect on the M50% from altering the starch concentration, (Table 4.6), shows that this mechanism was not suitable to account for any of the actions of starch in these formulations. p22

Increasing the compaction pressure caused a significant increase in the M50% (Tables 4.6 and 4.6c). A similar result was reported by Fukuoka et al. (1983) with microcrystalline cellulose tablets mixed with magnesium stearate, and although a direct comparison cannot be made, the rates of liquid penetration were of a similar order to those of the present study. The reduction in the rate of liquid uptake was probably simply due to the increased level of bonding induced by closer particle-to-particle proximity. The release of microcrystalline cellulose bonds due to hydration would therefore take longer due either to an increased number of bonds to be broken or an increased bond strength.

The M50% values attributable to the interaction between mixing time and drug particle size are presented in Table 4.6d. This indicates that the effects of the single factors were reitterated i.e. an increase in the M50% with either a larger drug size or a longer mixing time. The interaction was significant because of the exaggerated M50% with the large particle size, long mixing time combination. This indicates that the mechanisms controlling the M50% changed with this combination of treatments. The main possible mechanisms some described above were the liquid path length extension and reduced porosity with the larger drug particle size and the hydrophobic barriers created by an increased distribution of magnesium stearate. With a ~~The~~ combination of a ~~the~~ larger drug size fraction and a long mixing time, the longer mixing time may have emphasised the liquid path lengthening due to the larger drug crystals, leaving very few continuous Avicel matrix routes for the liquid to travel along. This accounts for an increase in M50% but not to the extent shown in Table 4.6d. However, if the combination of mechanisms was sufficient to form continuous hydrophobic barriers, then there would be no direct route for liquid penetration until either the paracetamol crystals started dissolving or some disruption of the hydrophobic barrier occurred e.g. by swelling starch grains. Thus the lengthening of the M50% would have been exaggerated.

The 3 factor interaction between mixing time, drug particle size and compaction pressure was ~~is~~ also significant (Table 4.6). Table 4.6e shows the mean M50% attributable to the individual combinations of treatments. It can be seen that the only combination not following the trends of the individual factors was the M50% attributable to the small drug particle size, the highest pressure and the shorter mixing time. This suggests that between the medium and high pressures some additional process affecting the penetration took place, which was suppressed by either increasing the mixing time or the particle size. It is difficult to understand why this should have occurred but one possibility relates to the mixing process itself. In the preceding discussions the effect of increasing the mixing times has been considered largely in terms of increasing the distribution of lubricant over particle surfaces with its consequences of a reduction in bond strengths and increased hydrophobicity. However an increased mixing time will also increase the homogeneity of a mixture, indeed this is the reason for the mixing process. Therefore a shorter mixing time may be assumed to produce a less homogenous mix. With the smaller sized fraction of paracetamol there was a tendency for the particles to aggregate, thus it may be postulated that the aggregates existed in the shorter mixing time formulations. The degree of aggregation may also be presumed to be less where the electrostatic forces holding them together have been ameliorated by the lubricant altering the surface of the drug or by simple particle to particle attrition i.e. by a longer mixing time or by the reduction in specific surface area and greater particle mass with the larger drug fraction. When a powder is compacted, after the initial packing the particles in the powder are forced into close proximity with varying degrees of elastic and plastic deformation until bonds form. In this particular case when the local pressure on an electrostatically held aggregate became sufficiently high, the aggregate may have been broken down either due to the stress imposed on the structure as a whole or because of local intrusions of plastically deforming particles around it. As far as liquid penetration is concerned the effects would be the same. A hydrophobic barrier at lower compaction pressures (the aggregate) thus becomes a series of hydrophobic inclusions in the matrix at a higher pressure. The critical factor determining the M50% being the additional path length necessary to bypass a large hydrophobic surface. Therefore, if breakdown of aggregate structures is assumed to take place between $150MNm^{-2}$ and $200MNm^{-2}$ then a reduction in the M50% would be expected. This would not necessarily alter the tablet porosity if the aggregate were assumed to be a close rather than a loose structure, it would however increase the tablet tensile fracture stress with the removal of large potentially stress* tablet. An examination of Table 4.4e tends to support this hypothesis, even though this table does not represent a significant interaction.

* focusing inclusions ie weaker parts of the

4.7. Statistical Analysis of the Treatments Relating to the Dissolution of Paracetamol from Tablets.

The ANOVA table for the dissolution of paracetamol as represented by the time for 90% of the drug to dissolve (T90%) is given in Table 4.7. Tables 4.8 and 4.9 are the ANOVA tables based on the times for 50% and 60% of the drug to dissolve, both of which are similar to Table 4.7. The ANOVA of the T90% corrected for a constant lag time (Section 2.6.2) is identical to Table 4.7, the only differences between the corrected and uncorrected analyses being in the mean attributable T90%, each figure of which is reduced by the correction factor.

p 81 82

The most significant treatment affecting the T90% was the starch concentration (Table 4.7). The mean T90% attributable to the different starch concentrations are shown in Table 4.7a. This shows that increasing the starch concentration decreased the T90%. This result was not unexpected as starch is normally used for its disintegrant action. However Avicel is also reported to have disintegrant properties (Gissinger and Stamm 1980) and this shows that starch, which replaced Avicel in the high starch formulations, enabled dissolution to take place faster than with Avicel.

√

The effect of altering the particle size of the drug was significant (Table 4.7) and the reverse of what would be expected from Equation 1.8 (Table 4.7b). The interaction between starch concentration and drug particle size was also significant, (Tables 4.7 and 4.7c). Table 4.7c shows that the effect of altering the drug particle size on the T90% was more marked at the

p26

TABLE 4.7.

ANOVA table based on the time for 90% of the drug to dissolve from paracetamol tablets.

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	0.23	17.34	1.47
STARCH	1	64.25	4884.91	413.57 ***
SIZE	1	13.75	1045.44	88.51 **
PRESSURE	2	0.78	29.48	2.50
MIXTIME.STARCH	1	0.05	3.53	0.30
MIXTIME.SIZE	1	0.27	20.17	1.71
STARCH.SIZE	1	8.32	632.43	53.54 **
MIXTIME.PRESSURE	2	0.48	18.37	1.56
STARCH.PRESSURE	2	0.63	24.04	2.04
SIZE.PRESSURE	2	2.32	88.34	7.48
MIXTIME.STARCH.SIZE	1	5.75	436.91	36.99 **
MIXTIME.STARCH.PRESSURE	2	0.78	29.83	2.53
MIXTIME.SIZE.PRESSURE	2	0.21	8.15	0.69
STARCH.SIZE.PRESSURE	2	1.86	70.81	6.00
RESIDUAL	2	0.31	11.81	
TOTAL	23	100.00	330.54	

GRAND MEAN 22.92 min

TOTAL NUMBER OF OBSERVATIONS 24

SIGNIFICANCE LEVEL *** >99% , ** >97.5%

continued

Table 4.7a.
The mean T90% attributable to the starch concentration.

	starch concentration (%)	
	1	7
T90% (min)	37.18	8.65

Table 4.7b.
The mean T90% attributable to the drug particle size.

	drug particle size (μm)	
	-20	+20
T90% (min)	29.52	16.32

continued

Table 4.7c.

The mean T90% (min) attributable to the interaction between starch concentration and drug particle size.

		starch concentration (%)	
		1	7
drug particle size (μm)	-20	48.92	10.12
	+20	25.45	7.18

Table 4.7d.

The mean T90% (min) attributable to the interaction between starch concentration, mixing time and drug particle size.

		starch concentration (%)			
		1		7	
mixing time (min)		1	5	1	5
drug particle size (μm)	-20	44.97	52.87	13.93	6.30
	+20	31.87	19.03	4.30	10.07

TABLE 4.8.

ANOVA Table based on the time for 50% of the drug to dissolve from paracetamol tablets.

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	0.00	0.02	0.03
STARCH	1	63.68	308.73	413.04 ***
SIZE	1	14.76	71.58	95.76 **
PRESSURE	2	0.36	0.87	1.17
MIXTIME.STARCH	1	0.00	0.01	0.01
MIXTIME.SIZE	1	0.00	0.02	0.03
STARCH.SIZE	1	11.77	57.08	76.36 **
MIXTIME.PRESSURE	2	0.31	0.74	0.99
STARCH.PRESSURE	2	0.55	1.34	1.79
SIZE.PRESSURE	2	2.26	5.49	7.34
MIXTIME.STARCH.SIZE	1	2.43	11.80	15.79
MIXTIME.STARCH.PRESSURE	2	0.37	0.90	1.21
MIXTIME.SIZE.PRESSURE	2	0.45	1.10	1.47
STARCH.SIZE.PRESSURE	2	2.73	6.61	8.85
RESIDUAL	2	0.31	0.75	
TOTAL	23	100.00	21.08	

GRAND MEAN 6.88 min

TOTAL NUMBER OF OBSERVATIONS 24

SIGNIFICANCE LEVEL *** >99%; ** >97.5%

TABLE 4.9.

ANOVA Table based on the time for 60% of the drug to dissolve from paracetamol tablets.

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO	
MIXTIME	1	0.00	0.02	0.01	
STARCH	1	61.32	622.20	247.60	***
SIZE	1	15.28	155.04	61.70	**
PRESSURE	2	0.54	2.72	1.08	
MIXTIME.STARCH	1	0.00	0.04	0.02	
MIXTIME.SIZE	1	0.06	0.60	0.24	
STARCH.SIZE	1	11.89	120.60	47.99	**
MIXTIME.PRESSURE	2	0.31	1.58	0.63	
STARCH.PRESSURE	2	0.76	3.85	1.53	
SIZE.PRESSURE	2	2.42	12.26	4.88	
MIXTIME.STARCH.SIZE	1	3.36	34.08	13.56	
MIXTIME.STARCH.PRESSURE	2	0.48	2.42	0.96	
MIXTIME.SIZE.PRESSURE	2	0.42	2.15	0.86	
STARCH.SIZE.PRESSURE	2	2.68	13.59	5.41	
RESIDUAL	2	0.50	2.51		
TOTAL	23	100.00	44.12		

GRAND MEAN 9.01 min

TOTAL NUMBER OF OBSERVATIONS 24

SIGNIFICANCE LEVEL *** >99% , ** >97.5%

lower starch concentration, where the decrease in T90% due to the particle size (24 min), may be seen to be almost as great as the overall effect of increasing the starch concentration (29 min, Table 4.7a).

Mixing time had no significant effect on the T90% (Table 4.7), which implies that the presence of magnesium stearate between particles played little part in the dissolution process. The rapid liquid penetration into the microcrystalline cellulose matrix may be modified by the presence of magnesium stearate as is shown in Table 4.6, but the drug surface was not rendered more hydrophobic or the T90% would have been significantly increased with a longer mixing time. The starch surface should be made more hydrophobic with an increased lubricant distribution. Thus the initial penetration of the starch grain may be inhibited by the magnesium stearate but once the liquid passes the hydrophobic barrier swelling of the grain will take place disrupting the barrier layer and allowing liquid to enter the grain at a higher rate. 'cos more liquid has become available in the pause.

Gissinger and Stamm (1980) studied the rate and extent of the swelling of maize starch. They found that the maximum swelling of 103% occurred in 3 minutes in a starch tablet. Applying these figures to the present study with a tablet volume of about $1cm^3$ X, a minimum porosity (Table 3.7) of 12%, a maximum starch concentration of 28mg per 400mg tablet and the density of starch being $1.47gcm^{-3}$, it can be calculated that the maximum expansion could almost be accommodated by the void space. The action of starch in these formulations is therefore unlikely to be due to its expansion directly disrupting the tablet matrix and thus increasing the surface available for dissolution, although localised

0.35cm³

disruption may occur. Fukuoka et al. (1983) and Lerk et al. (1979) deduced that microcrystalline cellulose particles split apart when hydrated due to the breakage of hydrogen bonds creating large pores available for liquid ingress. This process is likely to occur more rapidly than the hydration of starch grains because it is self sustaining, that is, as the pores open more liquid can enter to break more bonds and allow the pores to open further. Considering the tablet as a whole, the hydration of starch grains must occur at a later stage than the hydration of Avicel because a large proportion of the starch grains have no liquid contact until the liquid has hydrated the Avicel surrounding it.

see also
18, 23, 169

The explanation of the increase in dissolution rate (shorter T90%) with increased starch concentration may relate to the particle surface characteristics rather than any disintegrant action. The mechanism of surface interaction between paracetamol and microcrystalline cellulose is not known but is likely to be deficient in hydrogen bonds compared to joined microcrystalline cellulose surfaces. Thus liquid will be preferentially wicked through the microcrystalline cellulose matrix. Where liquid does penetrate along the paracetamol--Avicel interface a similar phenomenon may occur, with the Avicel peeling away from the hydrophobic drug surface. This would result in a pore with one hydrophobic and one hydrophilic side, in which case water would tend to penetrate back into the hydrophilic side. When the starch grains in contact with the paracetamol surface hydrate, the grains have no similar tendency to separate, thus the drug-starch interface is rendered more hydrophilic allowing the liquid to wet the paracetamol surface and dissolution to take place.

penetration
channel

starch holds water in place

The greater the concentration of starch, the greater the area of hydrophilic drug surface available for dissolution rather than the relatively hydrophobic unmodified drug surface which resists wetting.

Table 4.7c implies that, at the higher starch concentration, sufficient starch was in contact with the drug to render most of the drug surface hydrophilic irrespective of the drug particle size. A calculation of the ratios of surface areas of starch and paracetamol is shown in Table 4.10. The similarity between the surface area ratio and the T90%, bearing in mind that the T90% is in minutes and the surface area ratios are dimensionless numbers, supports the theory that the T90% was related to the ratio of drug:starch surface area. It should be noted that the T90% represents an inverse rate of dissolution i.e. the greater the T90% the slower the dissolution rate of the drug. For this reason the ratios of surface area are presented in the calculation as drug area per unit starch area, a greater ratio under this hypothesis representing a reduction in the potential hydrophilic surface and thus a slower dissolution rate.

The interaction of mixing time, starch concentration and drug particle size was also significant (Table 4.7), but at a lower probability than the factors discussed above. The mean T90% values attributable to the various combinations of factors are shown in Table 4.7d. As this interaction is of relatively low significance it will not be explored here but may be taken as an indication that if the levels of factors were different then a more significant interaction may indeed be present. This would probably be an effect of the distribution of low levels of starch by longer

Table 4.10
The Theoretical Ratio of Surface Areas of Paracetamol and Starch.

1. Derivation:-

	Diameter	Density	Formln. Percent	Surface Area per particle	Particle Volume	Total Volume	Number of particles	Total Surface.
units	µm	gcm^{-3}	%	$µm^2$	$µm^3$	cm^3	$x10^9$ /100g	$µm^2x10^9$ /100g
paracetamol +20	20.4	1.29	25	1307.4	4445.2	19.37	4.356	5696
paracetamol -20	7.3	1.29	22.8	167.4	203.7	17.66	86.704	14516
starch	14.0	1.47	1	615.8	1436.8	0.68	0.474	292
starch	14.0	1.47	7	615.8	1436.8	4.77	3.317	2042
notes	(A)	(B)		(D)	(D)	(C)	(E)	(F)

NOTES;

A. mean surface volume diameter (Table 3.2)
C. weight/density; volume per 100g formulation.
E. total volume/particle volume

B. Table 2.3
D. Assuming spherical particles
F. Surface area per particle x number of particles

$\frac{4}{3}\pi r^3$ $4\pi r^2$

2. Summary and Comparison with Table 4.7c:-

Drug Particle Size µm	Starch Concentration %	Surface Area Ratio Drug Area/Starch Area (final column above)	T90% (from Table 4.7c) min
-20	1	49.7	48.91
+20	1	19.5	25.45
-20	7	7.1	10.11
+20	7	2.8	7.17

mixing times increasing the probability of starch-drug interactions.

The effect on the T90% of increasing the compaction pressure was not significant (Table 4.7). This again supports the hypothesis that the dissolution process was controlled by the starch-drug interaction. An increase in compaction pressure would undoubtedly cause some plastic deformation of the starch and drug, and an overall increase in contact area between all of the particles in the tablet. However, if the dissolution of the drug is controlled by the rate of liquid transfer across the starch grains, then, until a significant permanent increase in the contact area of the starch took place, the dissolution rate of the drug would not increase. Danielson et al. (1983) found that only poor tablets of starch USP could be made, the stresses developed by elastic recovery being sufficient to break the bonds formed during compaction, this indicates that although plastic deformation of starch takes place it does not necessarily imply an increase in contact area.

4.8. The Relationship Between Tensile Fracture Stress and T90% in Paracetamol Tablets.

The relationship between the tensile fracture stress and the time for 90% drug dissolution may not strictly be analysed by the standard linear regression method as the variables were not from normally distributed populations. An analysis of covariance is not subjected to this constraint and allows an examination of the relationship. The reduction in the percentage sum of squares gives an indication of the correlation between the variables. In this case there were 17% of the sum of squares remaining to the variate, T90%, after the removal of the effect of the covariant, tensile fracture stress. This may be interpreted as indicating that there was some relationship between the T90% and the tensile fracture stress. As can be seen from the scatter diagram (Figure 4.2), this can be summarised as a high T90% being associated with a high tensile fracture stress. The significant treatments common to both the T90% and the tensile fracture stress were the drug particle size and the starch concentration. A smaller drug particle size resulted in an increase in the T90% and an increase in the tensile fracture stress (Tables 4.7b and 4.4b). Likewise a lower starch concentration resulted in an increase in the T90% and an increase in the tensile fracture stress (Tables 4.7a and 4.4c). The mechanisms involved in each case have been discussed above where the tensile fracture stress was postulated to be a result of the reduction in bonding due to magnesium stearate distribution and the T90% due to the surface interaction between starch and paracetamol. Under these hypotheses there would not appear to be any basis for any dependence of the T90% on the tensile fracture stress. The covariance analysis therefore probably reflects the coincidence of significant factors i.e. purely a facet of the way the experiment was designed.

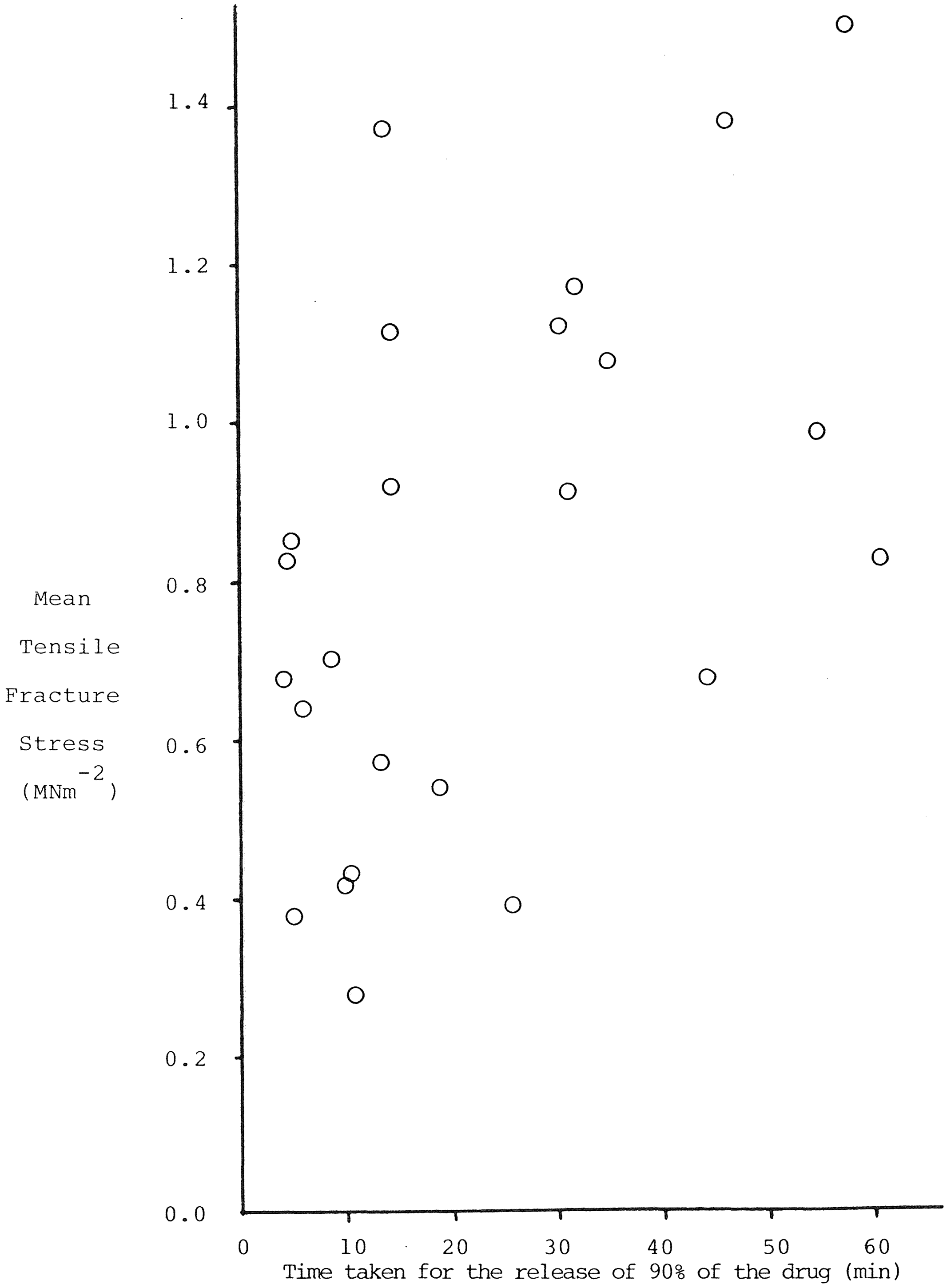


Figure 4.2

Scatter diagram of the mean T90% for each batch of paracetamol tablets and the associated mean tensile fracture stress.

4.9 A Summary of the effects of the treatments on the characteristics of paracetamol tablets.

This section is an examination of the treatments and their effects on paracetamol tablets. It is a summary of the mechanisms discussed in the previous sections in Chapter 4 from the viewpoint of the treatment rather than the determinant.

4.9.1 The Effect of a Longer Mixing Time.

An increase in the mixing time resulted in an increase in the tablet porosity and the time needed to attain 50% liquid uptake (M50%). It produced a decrease in the tensile fracture stress, but had no significant effect on the drug release (T90%). The mixing time was involved in significant interactions with the drug particle size when the porosity or the M50% were examined. wtcv↓

The principal effect of increasing the mixing time was an increase in the distribution of magnesium stearate over the particle surfaces. The magnesium stearate interferes in bond formation on compaction, renders hydrophilic surfaces more hydrophobic, reduces the effect of surface charges and may increase particle mobility by lubricating the surfaces. The interference in bond formation was seen in the reduction of the tensile fracture stress and the increase in porosity. The former being due to an overall decrease in bonding and the latter due to the decrease in bonding allowing elastic recovery to take place to a greater extent.

The reduction in hydrophilic surface was shown by the increase in M50%, the more hydrophobic surfaces retarding liquid penetration. The lack of effect on the T90% was particularly interesting, indicating that the drug surface was not significantly affected by the lubricant or the bonding within the tablet.

The effect of the mixing time on surface charges was shown in the interactions with the drug particle size. These interactions were seen when the porosity and the M50% were examined. It has been suggested that the smaller sized drug with a higher surface charge formed electrostatic bridging structures which increased the porosity in the tablets, but which were unable to form when the surface charge was dissipated by an increased distribution of magnesium stearate. This may have been facilitated by an increased surface lubrication of the particles, allowing particles to move more freely and not become locked into bridging structures.

4.9.2 The Effect of Increasing the Drug Particle Size.

wter ↓

Increasing the drug particle size decreased the tablet porosity, the tensile fracture stress ~~and~~ the T90%; it increased the M50% and the coefficient of weight variation. The effect of increasing the particle size whilst keeping the formula weight the same, was a reduction in the total surface area of the powder mix. The characteristics of the particles themselves may also be altered, this manifested itself mainly as a reduction in the electrostatic charge effects with the larger size fraction. The larger drug particles were therefore less cohesive and did not suffer from drug losses during mixing, (Table 3.6). One consequence of the loss of drug in the mixing of the smaller paracetamol fraction was a change in the ratio of drug to excipient. This has not been considered in the preceding discussion as it was inseparable from the effect of particle size. The influence of the increase in the excipient concentration with the smaller drug size fraction has therefore been highlighted in this section.

The decrease in the coefficient of weight variation, when the drug size was increased, was probably due to the increased weight of the drug particles. The resultant greater inertia of the drug particles carrying the excipient particles with them into the die and providing an initial consolidation. This was also shown by the decrease in porosity. A contributory factor may have been the reduction in surface which would have reduced any surface charge effects. These have been suggested to be involved in the formation of bridging structures when the powder was in the die. A larger drug particle will require greater electrostatic force to prevent it moving beyond the bridge formation point and will have proportionately less surface charge available to form temporary bonds. These actions were illustrated by the interaction between mixing time and drug particle size; the coefficient of tablet weight variation was greatest with the smaller particle size and the shortest mixing time. The electrostatic bridging being reduced either by increasing the particle size or the mixing time. In the latter case the charge leakage as a result of the distribution of lubricant may have been enhanced by the loss of drug during mixing. Surprisingly this was not shown with the tablet porosity, the lowest porosity being produced from the combination of the largest size and the shortest mixing

drug loss

time. This probably reflected the effectiveness of another mechanism, the reduction in bond formation induced by the distribution of magnesium stearate. This would allow more elastic recovery to take place within the compact such that the tablet porosity increases with a longer mixing time, thus ameliorating the electrostatic effects.

The decrease in the tensile fracture stress, when the drug particle size was increased, was probably simply due to the reduction in bonding surface available. This may have been exacerbated by a change in the drug crystal strength. The effect being due to the greater probability of weakening cracks in larger crystals. An increase in the concentration of Avicel with the smaller drug size fraction may also have contributed to a greater tensile fracture stress but this must have been a minor effect or the interaction between the particle size and mixing time would have been significant. The extent of drug loss during mixing being influenced by both the drug particle size and the mixing time, (Table 3.6). The smaller ~~drug~~ mix surface area would also result in an increase in the ratio of magnesium stearate to particle surface area. This would result in a greater concentration of lubricant between particles with an increased probability of interference in bonding.

drug loss

– when size increased

The M50% was longer with the larger size drug particles. This was probably due to the consolidation of hydrophobic surfaces which would extend the path length of liquid penetrating to the centre of the tablet. The interaction with mixing time tended to support this, when the retardation of penetration was increased with a greater distribution of magnesium stearate. The lower porosity may have augmented the effects of large hydrophobic barriers in the compacts by a reduction in the continuity of penetration channels. Again this may have been influenced by the drug losses involved with the smaller size drug, the higher proportion of hydrophilic excipients providing additional routes for liquid penetration.

The T90% was shorter with the larger drug particle size in contradiction to classical dissolution theory. These theories of dissolution relate the dissolution rate to the surface area of the solid. In this study it appeared that the surface area of the drug available for dissolution was considerably different to the area estimated from particle sizing studies. This may have been due to the hydrophobicity and wetting of the drug surface. The smaller specific surface area of the larger drug particles raises the ratio of the surface of the other excipients to that of the drug. It has therefore been postulated that the starch acts as a bridge over the hydrophobic surface barrier of the drug. Thus increasing the starch/drug surface ratio will increase the dissolution rate. The interaction between the drug particle size and the starch concentration when the T90% was examined tends to support this (Table 4.10). The slight reduction in tablet drug content with the smaller size fraction might have been expected to increase the dissolution rate by raising the proportion of hydrophilic excipients. Tables 4.7b and 4.7c suggest that this did not occur.

4.9.3 The Effect of Increasing the Starch Concentration.

Increasing the starch concentration resulted in an increase in the tablet porosity but a decrease in the tensile fracture stress. It produced a large decrease in the T90% and had little effect on the other determinants studied.

[illegible]

The starch was included in the formulation as a disintegrating agent. Its concentration was raised by substitution of the Avicel in the formulation. The Avicel particles were of smaller size than the starch particles such that the total surface area in the powder decreased with the higher starch concentration. The extent of elastic recovery of the starch was probably greater than that of the Avicel and it may have been intrinsically weaker.

A greater proportion of the larger sized starch grains in the powder may have altered the packing efficiency in the die sufficiently to result in an increased porosity. However a higher degree of elastic recovery, sufficient to break some of the bonds formed on compaction, would have resulted in an increase in the void space when the starch grains tried to regain their original shape from their distortion under peak compression. A reduction in the number or strength of permanent bonds formed during compression might be expected to reduce the tensile fracture stress of the compact. This did in fact occur, but the additional elastic recovery associated with a higher starch concentration may not have been the only cause. One of the other factors might have been the increase in interparticulate magnesium stearate as a consequence of

no – explain

the smaller particle surface area. Other contributary mechanisms may have included the possibility of the starch grains being weaker than the Avicel particles they replaced, the reduction in surface was available for bonding and that less surface was available for cohesive rather than adhesive bonding. The combination of determinants cannot be excluded, that is, a change in porosity by whatever mechanism may influence the tensile fracture stress.

Increasing the starch concentration did not significantly affect the M50% but decreased the T90%. The obvious explanation would appear to be the disintegrant action of the starch. However, a simple expansion of the starch grains on hydration of about 4 times that recorded by Gissinger and Stamm (1980) would have been necessary to fill the void space in the tablet. This does not mean that the starch did not act as a disintegrant, but that simple expansion was unlikely to be the major cause of any disintegration. The alternative theories of disintegration such as the heat of hydration causing air expansion or active repulsion of particles were also discounted as the principal action of an increased starch concentration on the T90%. The basis for this has been postulated to lie in the classical dissolution theories where the rate of dissolution has been shown to depend on the surface area of the solid. If the starch acted solely as a disintegrant then there would be a lag time in the dissolution process whilst the compact disintegrated followed by a surface area dependent solution of the solid. The lag time would depend on the starch concentration. The dissolution profiles in Figures 3.2 to 3.9 show no such marked difference in lag time with starch concentration. The conclusion was therefore that

103%

only just

No

[illegible]

the surface area of drug available for dissolution (effective surface area) was not affected by any disintegration taking place. This was supported by the effect of altering the drug particle size which showed that the larger sized drug dissolved faster than the smaller. This indicated that the effective surface area of the large size drug was greater than that of the smaller size. The interaction between the particle size and the starch concentration showed that the effect of the drug particle size was more marked at the lower starch concentration. The situation has been resolved by the hypothesis that the main action of the starch is to overcome the hydrophobic barrier to the initial wetting of the drug surface. Under this hypothesis the ratio of the drug surface area to the starch surface area would be the principal influence on the T90%. The similarity between these ratios and the T90% is shown in Table 4.10.

4.9.4 The Effect of Increasing the Compaction Pressure.

An increase in the compaction pressure resulted in a decrease in the tablet porosity, the tensile fracture stress and the M50%. It had no significant effect on the other determinants studied. The effect of a higher compaction pressure is simply to increase the proximity of particles. It will bring surfaces together and possibly distort the particles to the extent of inducing elastic or plastic deformation around other particles or, for a small proportion of particles, against the punches or die wall. As the pressure distribution is not homogenous in the compact the forces acting on individual particles may be vastly different. The lower porosity was therefore due to the

wtcv O
+ fs ↑
M50 ↑

particle surfaces being forced closer together with a greater probability of forming bonds. The extent of bond formation whilst the particles are subject to the compression forces does not necessarily reflect the bonds remaining after ejection of the compact from the die. During ejection residual forces may act on the compact, particularly the force developed by the die wall attempting to recover from its distortion during compression of the powder. In the extreme state this radial force may induce lamination of the compact. Those particles, or parts of particles, which were not stressed above their elastic limit will also be exerting forces of elastic recovery against some of the bonds formed during compaction. Thus there ~~will~~ may be a net increase in permanent bonding as a result of increasing the compaction pressure. As the particles were held in closer proximity the porosity was reduced. The tablet strength measured as the tensile fracture stress was determined by the same mechanisms. However the increase in the tensile fracture stress was not proportional to the compaction pressure. This probably reflected the change in the balance of forces forming bonds and those breaking them after the compressive force was released. That is, the energy stored as bonds tended to a maximum as the energy delivered by compaction increased. The residual forces therefore increased and acted against the bonds formed to a progressively greater extent. This is no doubt a considerable simplification of the actual processes affecting the compact but would fit the observed results. The conclusion being that the lamination point was being approached at the highest compaction pressure, although no stress concentrating factor was sufficiently active to precipitate lamination. The lack of suitability of the friability test was a direct consequence of this with some tablets actually laminating during this test. It was perhaps surprising that there was little problem with the type of failure during diametral compression testing. Some tablets did show signs of lamination, but these were excluded from the results. The remainder apparently failed in tension.

The M50% was longer with a higher compaction pressure. This was probably due to a combination of the particles being closer together, restricting any channels for liquid penetration, and an increase in bonding of the Avicel particles. Microcrystalline cellulose (Avicel) has been found to ´peel apart´ on hydration leading to a more rapid rate of liquid penetration than explained by capillary action (Lerk et al. 1979). This enhanced liquid penetration would have been reduced where the Avicel was unable to open due to surrounding bonds holding the particles more tightly in position.

See also p18, 23, 169, 226

The lack of effect of the compaction pressure on the T90% lent support to the theory that the T90% was controlled by the effects occurring at the drug surface rather than in the tablet matrix. A higher compaction pressure reduced the rate of liquid penetration into the tablet. An increased level of bonding might have been expected to retard the effects of any disintegrants in the formulation, at least until the hydration of the disintegrant had developed sufficient force to break the additional bonding. The compression force may thus be assumed to have had no significant effect on the interaction between the starch and drug surface. This may in turn suggest that either the elastic limit of the starch was not exceeded and the starch grains were able to regain their original shapes or that the drug/starch interaction was not dependent on the area of contact but only on the presence or absence of contact.