CHAPTER 5.

THE STATISTICAL ANALYSIS OF THE RESULTS DERIVED FROM ASPIRIN TABLETS.

5.1 Introduction.

This chapter describes the results of the analysis of variance (ANOVA) of a factorially designed experiment based on the manufacture of aspirin tablets and discusses the mechanisms involved. The terminology described in Section 4.1 is used in this chapter. The values of determinants in the subsidiary (suffixed) tables refer to the mean value attributable to a treatment, that is, the sum of the values associated with a particular level of a treatment (or treatments), divided by the number of values involved, in the units of the original measurement.

The formulations and results on which these analyses were based are given in Chapter 3. It should be noted that the particle size of the drug used in these tablets was considerably larger than any of the excipients. Therefore, although the choice of drug particle size as a treatment in the statistical analyses is acceptable in itself, the levels used mean that only highly significant effects would be apparent. The combination of particles of grossly different sizes in a formulation for direct compression reflects a potentially poor formulation with a great propensity for segregation. The only situation where large and small particle size ingredients produce a good direct compression formulation is where ordered mixing takes place. That is, where the active ingredient coats the excipient particles. This experiment was therefore undertaken to test the application of the mechanisms derived in Chapter 4 to a considerably different formulation.

5.2 The Analysis of Variance based on the Coefficient of Weight Variation of Aspirin Tablets.

The analysis of variance (ANOVA) based on the coefficient of weight variation of aspirin tablets is shown in Table 5.1. None of the treatments were significant which suggests that the error attributable to the experiment was too high to identify any variation due to individual treatments. This may be viewed as the values of the coefficient of weight variation being distributed at random throughout the experimental batches of tablets. This indicates that the flow of powder into the die was unaffected by the mixing process or any changes in formulation, and was probably due to the large drug crystals carrying the smaller excipient particles into the die. The inertia of the drug crystals being sufficient to break up or prevent the formation of any temporary bridging structures formed by the excipients in the hopper or die. The small range and low values of the coefficient of weight variation (0.8-3.3%, Table 3.8) tend to suggest that there was little segregation of the drug particles. The combination of large and small particle sizes in these direct compression formulations did not therefore produce the expected particle segregation and this may therefore be considered to be an acceptable formulation.

TABLE 5.1

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

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	4.24	0.271	0.49
STARCH	1	0.06	0.004	0.01
SIZE	1	10.67	0.681	1.23
PRESSURE	2	5.39	0.172	0.31
MIXTIME.STARCH	1	0.00	0.000	0.00
MIXTIME.SIZE	1	4.16	0.266	0.48
STARCH.SIZE	1	8.36	0.534	0.97
MIXTIME.PRESSURE	2	16.85	0.538	0.97
STARCH.PRESSURE	2	3.76	0.120	0.22
SIZE.PRESSURE	2	11.87	0.379	0.69
MIXTIME.STARCH.SIZE	1	0.08	0.005	0.01
MIXTIME.STARCH.PRESSURE	2	7.05	0.225	0.41
MIXTIME.SIZE.PRESSURE	2	8.80	0.281	0.51
STARCH.SIZE.PRESSURE	2	1.41	0.045	0.08
RESIDUAL	2	17.30	0.552	
TOTAL	23	100.00	0.278	

GRAND MEAN 1.33%

TOTAL NUMBER OF OBSERVATIONS 24

NO SIGNIFICANT TREATMENTS

5.3 The Analysis of Variance based on the Porosity of Aspirin Tablets.

The ANOVA based on the porosity of aspirin tablets is shown in Table 5.2. The most significant treatment was an increase in compaction pressure which decreased the mean attributable tablet porosity (Table 5.2a). This was due to the closer proximity of particles on compaction being sustained on ejection of the tablet by either a greater bond strength per unit area of contact or a greater area of contact between particles. The increased contact area being the most likely because a greater proportion of particles would be subjected to forces above their elastic limit, allowing particles to deform plastically around each other to a greater extent thus increasing the area of permanent contact.

A longer mixing time produced a significant increase in porosity (Tables 5.2 and 5.2b). This was almost certainly due to the interference in bonding of magnesium stearate, which allowed elastic recovery of the particles to take place after compaction. The elastic recovery with the shorter mixing time being inhibited by the formation of stronger or more bonds during compaction. The lack of significance of increasing the starch concentration (Table 5.2) tends to indicate that any additional elastic deformation of starch had little effect compared to the elastic component of the deformation of the Avicel it replaced.

TABLE 5.2

ANOVA table based on the porosity of aspirin tablets.

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	19.40	13.41	71.31 **
STARCH	1	0.65	0.45	2.39
SIZE	1	0.05	0.03	0.17
PRESSURE	2	71.86	24.83	132.06 ***
MIXTIME.STARCH	1	0.17	0.12	0.62
MIXTIME.SIZE	1	0.03	0.02	0.11
STARCH.SIZE	1	0.04	0.02	0.13
MIXTIME.PRESSURE	2	0.89	0.31	1.63
STARCH.PRESSURE	2	0.19	0.06	0.34
SIZE.PRESSURE	2	0.03	0.01	0.05
MIXTIME.STARCH.SIZE	1	0.27	0.19	1.00
MIXTIME.STARCH.PRESSURE	2	4.78	1.65	8.78
MIXTIME.SIZE.PRESSURE	2	0.36	0.13	0.67
STARCH.SIZE.PRESSURE	2	0.75	0.26	1.38
RESIDUAL	2	0.54	0.19	
TOTAL	23	100.00	3.01	

GRAND MEAN 11.90%

TOTAL NUMBER OF OBSERVATIONS 24

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

continued

Table 5.2a.
The mean tablet porosity attributable to the compaction pressure.

	compaction pressure (MNm^{-2})		
	100	150	200
porosity (%)	13.93	11.05	10.73

Table 5.2b.
The mean tablet porosity attributable to the mixing time.

	mixing time (min)	
	1	5
porosity (%)	11.15	12.65

5.4 The Analysis of Variance based on the Tensile Fracture Stress of Aspirin Tablets.

Table 5.3 shows the ANOVA based on the tensile fracture stress of aspirin tablets. The most significant treatment was the mixing time, where a longer time produced a reduction in the mean attributable tensile fracture stress (Table 5.3a). This was almost certainly due to the increased spreading of magnesium stearate over the particle surfaces with a concomitant reduction in the bonding between particles on compaction (Lerk et al. 1979). The tablet porosity was greater with a longer mixing time (Table 5.2b). This was probably a consequence of the reduction in bonding, with elastic recovery being better able to take place after compaction where there were fewer restraining bonds formed. An increased mixing time would also increase the distribution of starch grains. If the elastic recovery of the starch is greater than that of the Avicel then this would contribute to the reduction in bonding, the additional movement on recovery breaking some of the bonds formed on compaction. However, the lack of significant effect of the starch concentration on the porosity, suggests that this latter possibility was unlikely.

Increasing the starch concentration significantly reduced the mean tensile fracture stress (Table 5.3b). This was probably due to the same mechanisms involved in altering the mixing time. The mean surface-volume diameter of the starch was greater than the Avicel it displaced in the formulation (Table 3.2). The higher starch concentration formulations will have a smaller total surface area for the lubricant to cover, resulting

TABLE 5.3

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

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	51.76	0.550	324.95 ***
STARCH	1	20.69	0.220	129.90 ***
SIZE	1	0.56	0.006	3.52
PRESSURE	2	19.39	0.103	60.88 **
MIXTIME.STARCH	1	0.37	0.004	2.33
MIXTIME.SIZE	1	0.27	0.003	1.71
STARCH.SIZE	1	0.46	0.005	2.92
MIXTIME.PRESSURE	2	0.40	0.002	1.25
STARCH.PRESSURE	2	0.84	0.004	2.65
SIZE.PRESSURE	2	2.67	0.014	8.38
MIXTIME.STARCH.SIZE	1	0.65	0.007	4.07
MIXTIME.STARCH.PRESSURE	2	1.22	0.007	3.84
MIXTIME.SIZE.PRESSURE	2	0.10	0.001	0.31
STARCH.SIZE.PRESSURE	2	0.29	0.002	0.90
RESIDUAL	2	0.32	0.002	
TOTAL	23	100.00	0.046	

GRAND MEAN 0.845 MNm^{-2}

TOTAL NUMBER OF OBSERVATIONS 24

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

continued

Table 5.3a.
The mean tensile fracture stress attributable to the mixing time.

	mixing time (min)	
	1	5
tensile fracture stress (MNm^{-2})	0.997	0.694

Table 5.3b.
The mean tensile fracture stress attributable to the starch concentration.

	starch concentration (%)	
	1	7
tensile fracture stress (MNm^{-2})	0.949	0.750

continued

Table 5.3c.

The mean tensile fracture stress attributable to the compaction pressure.

	compaction pressure (MNm^{-2})		
	100	150	200
tensile fracture stress (MNm^{-2})	0.714	0.906	0.915

Table 5.3d.

The mean tensile fracture stress (MNm^{-2}) attributable to the interaction between the starch concentration and the mixing time.

		starch concentration (%)	
		1	7
mixing time (min)	1	1.105	0.888
	5	0.777	0.611

in a greater interparticulate concentration of lubricant with a reduction in bond strength or number i.e a weaker tablet. Any elastic recovery of starch would reduce the bonding. Unfortunately little in the literature is available to substantiate this directly. Jones (1979) presented a graph of the elastic recovery for starch and Avicel which showed a greater elastic recovery for the starch. Paronen and Juslin (1983) and Krycer et al. (1982) derived the yield pressures of corn starch and Avicel respectively, from Heckel plots. These authors found that the yield pressures were 29.8MPa (Avicel) and 125MPa (starch), which whilst not directly related to elastic deformation, indicate that the elastic limit of Avicel will be exceeded at a much lower pressure than starch. As the stress distribution in compacts is not uniform (Train 1957) there were likely to be areas where the elastic limit of the starch was not exceeded even at the highest compaction pressure but where the elastic limit of Avicel was exceeded. Whilst yield pressures from Heckel plots only indicate the pressure at which plastic flow occurs and takes no account of any elastic component of deformation remaining after the initiation of plastic flow, they do indicate the pressure at which the initial elastic deformation is exceeded. It should also be noted that yield pressures determined under different experimental conditions, as in this case, should according to York (1979) be compared with caution. However the large difference between starch and Avicel may at least be taken to indicate that the yield pressure of Avicel is lower than that of starch. Hess (1978), in examining compact surfaces by scanning electron microscopy, observed that starch grains were frequently detached from adjacent particles. This may support the possibility that the elastic recovery of the starch affects the tablet strength.

Two other mechanisms may have been equally important in determining the reduction in the tensile fracture stress with an increased starch concentration. There was unfortunately no way of distinguishing between these mechanisms and the possibilities of a greater degree of elastic recovery or an increase in the interparticulate lubricant in the compact. One alternative mechanism was that the starch grains were inherently weaker than the Avicel particles, providing a weak area in the compact for the initiation of fracture. The other possibility was that the area available for bonding was reduced by the net reduction in surface area when the starch level was raised.

An increase in the compaction pressure resulted in a significant increase in the mean attributable tensile fracture stress (Table 5.3c). This was due to an overall increase in particle-particle proximity allowing greater bond formation. The increase in tensile fracture stress from 100-150MNm^{-2} was greater than from 150-200MNm^{-2}. This indicates that the tensile fracture stress was not linearly dependent on the compaction pressure and that a limiting tensile fracture stress was approached. This situation may be similar to that described by Groenwold et al. (1972) where a linear relationship between crushing strength and compaction pressure for cylindrical and flat bevelled edge tablets was observed up to a limiting value. At this point flat bevelled edge tablets laminated but cylindrical tablets merely failed to increase in strength. This was postulated to be caused by the stress concentration due to the bevelled edge; with the cylindrical tablets no such focus existed. The elastic recovery resulting in lamination of the bevelled edged tablets may therefore have taken place in the cylindrical tablets but without destroying

the tablet coherence. The tablet matrix would however have been weakened.

5.5 The Analysis of Variance based on the Friability of Aspirin Tablets.

The friability of a tablet is a measure of its ability to withstand mechanical handling determined by the weight loss induced by abrasive and impact forces. It is a much less precisely controlled test than a diametral compression test but nevertheless measures the strength of the bonding between particles subjected to stresses. It is not surprising therefore that the effects of the treatments on the tablet friability were similar to the effects on the tensile fracture stress.

The ANOVA relating to the friability of aspirin tablets is shown in Table 5.4. The mixing time, as with the tensile fracture stress, was the most significant treatment (Table 5.4a). The increased distribution of magnesium stearate and its interference in bond formation with a longer mixing time accounts for the increased friability, though the distribution of starch may also contribute to a reduction in bonding.

A higher starch concentration increased the friability (Table 5.4b). This was either a result of the increased elastic recovery of the starch or the greater concentration of interbond magnesium stearate due to the reduction in total surface area (compared to the Avicel which the starch replaced in the formulation). The interaction between starch concentration and mixing time

TABLE 5.4

ANOVA table based on the friability of aspirin tablets

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	31.11	2.305	614.05 ***
STARCH	1	15.81	1.171	312.01 ***
SIZE	1	0.66	0.049	13.04
PRESSURE	2	31.22	1.157	308.07 ***
MIXTIME.STARCH	1	4.06	0.300	80.08 **
MIXTIME.SIZE	1	0.78	0.058	15.45
STARCH.SIZE	1	0.30	0.023	6.01
MIXTIME.PRESSURE	2	4.50	0.167	44.42 **
STARCH.PRESSURE	2	2.84	0.105	28.03
SIZE.PRESSURE	2	3.79	0.141	37.43
MIXTIME.STARCH.SIZE	1	0.94	0.070	18.53
MIXTIME.STARCH.PRESSURE	2	2.40	0.089	23.67
MIXTIME.SIZE.PRESSURE	2	0.75	0.028	7.43
STARCH.SIZE.PRESSURE	2	0.74	0.027	7.30
RESIDUAL	2	0.10	0.004	
TOTAL	23	100.00	0.322	

GRAND MEAN 1.301%

TOTAL NUMBER OF OBSERVATIONS 24

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

continued

Table 5.4a

The mean friability attributable to the mixing time.

	mixing time (min)	
	1	5
friability (%)	0.99	1.61

Table 5.4b.

The mean friability attributable to the starch concentration.

	starch concentration (%)	
	1	7
friability (%)	1.08	1.52

Table 5.4c.

The mean friability attributable to the compaction pressure.

	compaction pressure (MNm^{-2})		
	100	150	200
friability (%)	1.74	1.10	1.07

continued

Table 5.4d.

The mean friability (%) attributable to the interaction between mixing time and starch concentration.

		starch concentration (%)	
		1	7
mixing time (min)	1	0.88	1.10
	5	1.28	1.94

Table 5.4e.

The mean friability (%) attributable to the interaction between mixing time and compaction pressure.

		mixing time (min)	
		1	5
compaction	100	1.26	2.22
pressure	150	0.87	1.32
(MNm^{-2})	200	0.84	1.30

(Table 5.4d), shows that there was an increase in friability when either the starch concentration was raised or the mixing time extended. The significance of the interaction arose from the combination of the higher levels of the two treatments which resulted in an exaggerated friability. This was probably a facet of the friability test itself, whereby the tablets were subjected to attrition from the fragments of tablets produced during the test. Thus, the greater the initial friability, the more exaggerated the percentage of the tablet lost during the test.

Increasing the compaction pressure was a significant treatment (Table 5.4) which resulted in a decrease in friability (Table 5.4c). This reflected the greater number of permanent bonds formed during the closer particle contact at the higher pressures. The difference between the friability attributable to the lower compaction pressure compared to the medium pressure was greater than the difference between the friabilities attributable to the medium and high compaction pressures. This was again similar to the tensile fracture stress (Table 5.3c).

Table 5.4e shows the interaction between the mixing time and compaction pressure. This shows the same trends as either the compaction pressure or the mixing time alone. The interaction was significant because of the larger difference between $100MNm^{-2}$ and $150MNm^{-2}$ with the longer mixing time compared to the shorter time. Again this may represent a problem with a friability test itself, that is, if there are powder losses from a tablet, the loose powder in the apparatus may impose additional stresses on the tablets. This probably explains the interaction, with the weakest tablets

(lowest pressure and longest mixing time) showing an exaggerated friability.

5.6 The Analysis of Variance based on the Liquid Uptake into Aspirin Tablets.

The time for 50% of the maximum liquid uptake (M50%) was used to represent the rate at which liquid penetrated the tablet, a high M50% indicating that penetration was slow. This was determined under different conditions to the dissolution test, in that it was carried out at room temperature with no liquid agitation. The rate of penetration measured in this test may therefore be expected to be slower than under the conditions of the dissolution test. The M50% thus provided a means of differentiating between the rates of liquid penetration in different formulations.

The ANOVA based on the liquid uptake into aspirin tablets is shown in Table 5.5. The most significant treatment was a longer mixing time, which decreased the mean attributable M50% (Table 5.5a). This was surprising as increasing the mixing time might have been expected to increase the distribution of hydrophobic magnesium stearate in the formulation, rendering more surfaces resistant to wetting and therefore retarding liquid ingress. The distribution of the lubricant has already been implicated in the reduction of tensile fracture stress with a longer mixing time (Section 5.4). An examination of the scatter diagram of M50% versus tensile fracture stress for aspirin tablets, (Figure 5.1), indicates that there was a strong relationship

TABLE 5.5

ANOVA table based on the liquid uptake into aspirin tablets.

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	42.88	31120.65	389.06 ***
STARCH	1	13.28	9638.13	120.49 ***
SIZE	1	2.36	1712.69	21.41
PRESSURE	2	9.42	3416.78	42.72 **
MIXTIME.STARCH	1	7.18	5213.00	65.17 **
MIXTIME.SIZE	1	2.55	1850.71	23.14
STARCH.SIZE	1	3.29	2385.46	29.82
MIXTIME.PRESSURE	2	4.01	1454.94	18.19
STARCH.PRESSURE	2	4.58	1662.35	20.78
SIZE.PRESSURE	2	0.43	154.52	1.93
MIXTIME.STARCH.SIZE	1	0.44	318.45	3.98
MIXTIME.STARCH.PRESSURE	2	7.91	2869.51	35.87
MIXTIME.SIZE.PRESSURE	2	0.83	299.59	3.75
STARCH.SIZE.PRESSURE	2	0.64	230.77	2.89
RESIDUAL	2	0.22	79.99	
TOTAL	23	100.00	3155.48	

GRAND MEAN 73.9 s

TOTAL NUMBER OF OBSERVATIONS 24

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

continued

Table 5.5a

The mean liquid uptake attributable to the mixing time.

	mixing time (min)	
	1	5
liquid uptake (s)	109.9	37.9

Table 5.5b.

The mean liquid uptake attributable to the starch concentration.

	starch concentration (%)	
	1	7
liquid uptake (s)	93.9	53.8

Table 5.5c.

The mean liquid uptake (s) attributable to the interaction between mixing time and starch concentration.

		starch concentration (%)	
		1	7
mixing time (min)	1	144.7	75.1
	5	43.2	32.6

continued

Table 5.5d.

The mean liquid uptake attributable to the compaction pressure.

	compaction pressure (MNm^{-2})		
	100	150	200
liquid uptake (s)	50.4	82.1	89.2

Table 5.5e.

The mean liquid uptake (s) attributable to the interaction between starch concentration, mixing time and compaction pressure.

		starch concentration (%)			
		1		7	
mixing time (min)		1	5	1	5
compaction	100	78.0	32.5	73.9	17.1
pressure	150	147.2	60.4	79.4	41.4
(MNm^{-2})	200	208.8	36.7	72.0	39.2

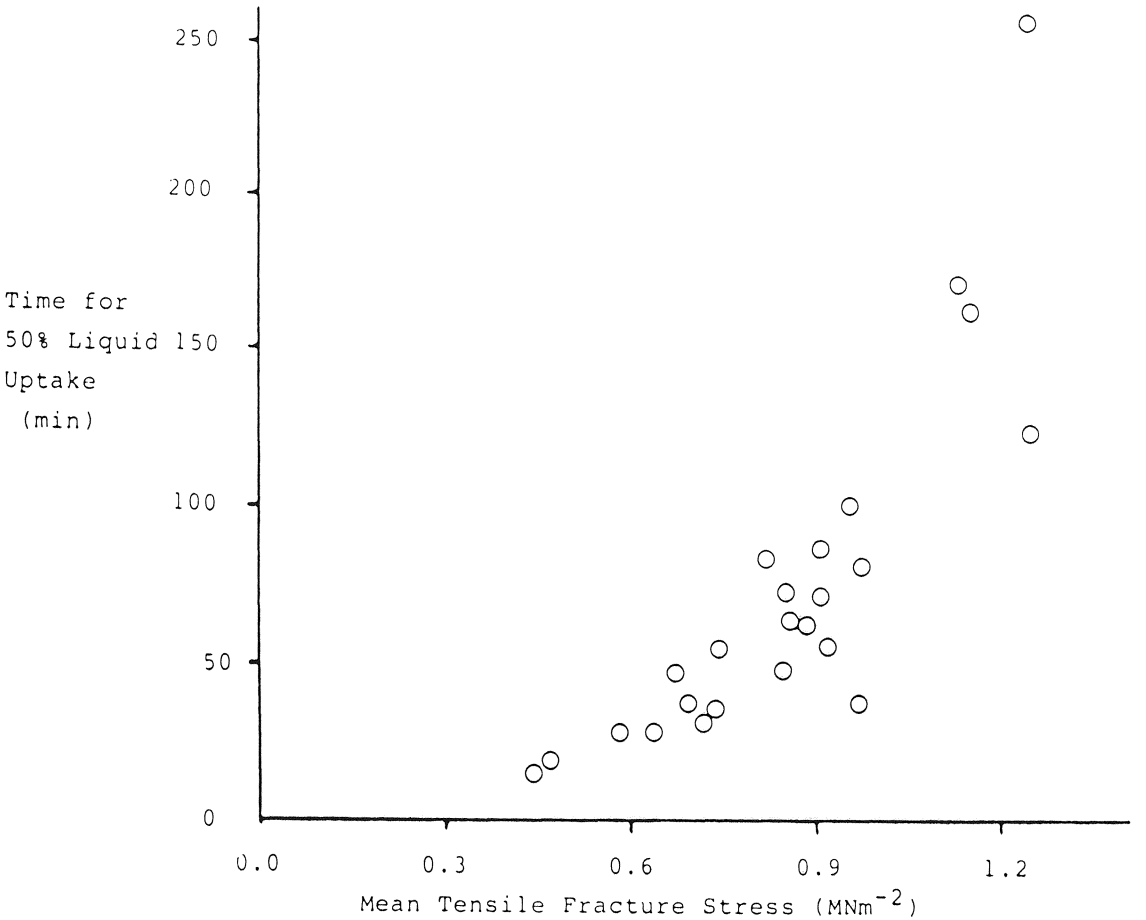

Figure 5.1

Scatter diagram of the mean liquid uptake (M50%) and the mean tensile fracture stress for each batch of aspirin tablets.

between these two determinants. The effect of increasing the starch concentration (Table 5.5b) or the compaction pressure (Table 5.5d) may similarly be accounted for by the same mechanisms as those affecting the tensile fracture stress discussed in Section 5.4. This leaves the question as to why the tensile fracture stress should have been related to the M50% sufficiently to overshadow the effects of individual treatments, e.g. the hydrophobic nature of magnesium stearate. The tensile fracture stress represents a measure of the bonding within a tablet. The longer M50% with a greater degree of bonding therefore suggests that the route of liquid penetration was between rather than across the particles. An increase in bonding resulting in a greater area of intimate particle contact and reducing the number of channels between particles. This could arise when continuous hydrophobic barriers exist in the tablet matrix such as large drug crystals combined with a hydrophobic lubricant.

The interaction between starch concentration and mixing time was significant and is shown in Table 5.5c. It can be seen that the M50% was not greatly changed by increasing the starch concentration with a long mixing time but was almost halved with a short mixing time. This follows the change in tensile fracture stress under the same treatments (Table 5.3d), that is, the weaker the tablet the shorter the M50%. This situation probably arose because the surface spreading of the magnesium stearate reduced the number of permanent bonds formed on compaction leaving channels for liquid transfer between particles. Thus where there was a smaller area of bonding within a compact i.e. a lower tensile fracture stress or higher friability, the liquid was able to

penetrate more rapidly. The increase in porosity with a longer mixing time (Table 5.2b) would also enhance liquid penetration according to this hypothesis. The interaction between the mixing time and the starch concentration was however significant when the M50% was considered but not when the tensile fracture stress was examined. The significance arose from the longer M50% with the combination of a short mixing time and a low starch concentration. This probably represents the effect of the relatively large hydrophobic areas in the tablet matrix, i.e. the drug crystals. Where the starch concentration was increased preferential liquid access routes were created. When the mixing time was increased the bonding was reduced again leaving channels for capillary penetration. With a short mixing time and a low starch concentration neither of these penetration mechanisms would be available. The liquid ingress in this case was probably directly through the hydrophilic excipients, i.e. the Avicel. Whilst this would have occured relatively fast through particular areas of the excipient due to the 'opening' of Avicel on hydration (Lerk et al. 1979), the large hydrophobic drug surfaces would tend to deflect the penetrating liquid back on itself, i.e. away from the centre. The low significance interaction between the mixing time, the starch concentration and the compaction pressure illustrates this further (Table 5.5e). An increase in compaction pressure would be expected to reduce the available penetration channels created by whatever cause. Thus the highest M50%, (lowest rate of liquid ingress), was shown with the highest compaction pressure, the shortest mixing time and the lowest starch concentration. When either the mixing time or starch concentration was increased, these effects became more important than changing the compaction pressure.

5.7 Statistical Analysis of the Treatments Relating to the Dissolution of Aspirin Tablets.

The dissolution of aspirin tablets was quantified by the time for 90% of the drug to dissolve (T90%). There are many ways of describing a dissolution profile, but the view of Goldsmith et al. (1978) was adopted in this study, i.e. model fitting does not generally contribute to the information obtained from the percent dissolved at given times. Whilst this figure does not define a dissolution profile, it is sufficient to differentiate between similar profiles such as those produced in this study. The ANOVA relating to the T90% of aspirin tablets is shown in Table 5.6. The ANOVAs derived from the T50% and T60% are shown in Tables 5.7 and 5.8. The most significant treatments with these determinants were the same as those of the T90%. The differences between these determinants relates to the value of the residual mean square which is the denominator in calculating the variance ratio. This represents the variation of the experimental results which was lower for the T50% and T60%. The reduced spread of the T50% and T60% compared to the T90% results thus accounts for the significance of some interactions for the T90% but not for the T50% or T60%. It should be noted that the significance reflects the probability that a given response does indeed exist. Hence the same trends were shown with the T50% and T60% as with the significant T90% interactions but without sufficient emphasis to raise the interaction above the experimental error. The following discussion is therefore restricted to the T90% which showed more, rather than less, significant interactions.

see 4.1 p146

TABLE 5.6

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

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO	
MIXTIME	1	19.95	4186.86	685.52	***
STARCH	1	36.25	7608.18	1245.71	****
SIZE	1	0.05	11.40	1.87	
PRESSURE	2	3.13	328.66	53.81	**
MIXTIME.STARCH	1	24.80	5205.97	852.39	***
MIXTIME.SIZE	1	0.16	33.64	5.51	
STARCH.SIZE	1	0.81	169.80	27.80	
MIXTIME.PRESSURE	2	5.20	545.34	89.29	**
STARCH.PRESSURE	2	5.44	571.01	93.49	**
SIZE.PRESSURE	2	0.76	79.98	13.10	
MIXTIME.STARCH.SIZE	1	0.52	108.82	17.82	
MIXTIME.STARCH.PRESSURE	2	2.54	267.11	43.74	**
MIXTIME.SIZE.PRESSURE	2	0.04	3.69	0.60	
STARCH.SIZE.PRESSURE	2	0.30	31.26	5.12	
RESIDUAL	2	0.06	6.11		
TOTAL	23	100.00	912.65		

GRAND MEAN 66.38 min

TOTAL NUMBER OF OBSERVATIONS 24

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

continued

Table 5.6a.

The mean T90% attributable to the starch concentration.

	starch concentration (%)	
	1	7
T90% (min)	84.2	48.6

Table 5.6b.

The mean T90% attributable to the mixing time.

	mixing time (min)	
	1	5
T90% (min)	79.6	53.2

Table 5.6c.

The mean T90% attributable to the compaction pressure.

	compaction pressure (MNm^{-2})		
	100	150	200
T90% (min)	59.0	70.4	69.8

continued

Table 5.6d.

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

		starch concentration (%)	
		1	7
mixing time (min)	1	112.1	47.1
	5	56.3	50.1

Table 5.6e.

The mean T90% (min) attributable to the interaction between starch concentration and compaction pressure.

		compaction pressure (MNm^{-2})		
		100	150	200
starch concentration (%)	1	67.2	94.5	90.8
	7	50.8	46.3	48.7

Table 5.6f.

The mean T90% (min) attributable to the interaction between the mixing time and the compaction pressure.

		compaction pressure (MNm^{-2})		
		100	150	200
mixing time (min)	1	63.2	90.7	84.9
	5	54.8	50.1	54.6

continued

Table 5.6g.

The mean T90% (min) attributable to the interaction between starch concentration, mixing time and compaction pressure.

		starch concentration (%)			
		1		7	
mixing time (min)		1	5	1	5
compaction	100	79.7	54.7	46.7	54.9
pressure	150	134.4	54.7	47.1	45.4
(MNm^{-2})	200	122.4	59.3	47.4	50.0

TABLE 5.7

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

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES %	MEAN SQUARES	VARIANCE RATIO
MIXTIME	1	22.51	324.22	439.07 ***
STARCH	1	52.39	754.43	1021.67 ****
SIZE	1	0.01	0.13	0.17
PRESSURE	2	1.60	11.56	15.65
MIXTIME.STARCH	1	14.06	202.44	274.16 ***
MIXTIME.SIZE	1	0.00	0.02	0.03
STARCH.SIZE	1	0.43	6.22	8.43
MIXTIME.PRESSURE	2	2.36	17.02	23.05
STARCH.PRESSURE	2	2.62	18.84	25.51
SIZE.PRESSURE	2	0.72	5.15	6.98
MIXTIME.STARCH.SIZE	1	0.09	1.34	1.81
MIXTIME.STARCH.PRESSURE	2	2.86	20.57	27.86
MIXTIME.SIZE.PRESSURE	2	0.07	0.52	0.70
STARCH.SIZE.PRESSURE	2	0.17	1.24	1.68
RESIDUAL	2	0.10	0.74	
TOTAL	23	100.00	62.61	

GRAND MEAN 20.95 min

TOTAL NUMBER OF OBSERVATIONS 24

SIGNIFICANCE LEVEL **** >99.9%; *** >99%

TABLE 5.8

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

SOURCE OF VARIATION	DEGREES FREEDOM	SUM OF SQUARES	%	MEAN SQUARES	VARIANCE RATIO	
MIXTIME	1	21.29		490.51	273.97	***
STARCH	1	48.93		1127.51	629.75	***
SIZE	1	0.04		0.84	0.47	
PRESSURE	2	1.76		20.32	11.35	
MIXTIME.STARCH	1	15.61		359.60	200.85	***
MIXTIME.SIZE	1	0.05		1.08	0.61	
STARCH.SIZE	1	0.66		15.20	8.49	
MIXTIME.PRESSURE	2	3.29		37.91	21.18	
STARCH.PRESSURE	2	3.50		40.28	22.50	
SIZE.PRESSURE	2	0.96		11.05	6.17	
MIXTIME.STARCH.SIZE	1	0.19		4.42	2.47	
MIXTIME.STARCH.PRESSURE	2	3.28		37.80	21.11	
MIXTIME.SIZE.PRESSURE	2	0.04		0.50	0.28	
STARCH.SIZE.PRESSURE	2	0.25		2.82	1.58	
RESIDUAL	2	0.16		1.79		
TOTAL	23	100.00		100.18		

GRAND MEAN 27.20 min

TOTAL NUMBER OF OBSERVATIONS 24

SIGNIFICANCE LEVEL *** >99%

The most significant treatment was the starch concentration, where an increase reduced the mean attributable T90% (Table 5.6a). With the maximum starch concentration of 7% and the minimum tablet porosity of approximately 10% (Table 3.8), the expansion of the starch on hydration must be at least 43% of its original volume to fill the available void space. A volume increase greater than this will exert forces on the surrounding particles, and provided that the hydraulic pressure of hydration is greater than the bonding forces holding the surrounding particles in the tablet matrix, then the tablet matrix will be disrupted. Even if the hydraulic pressure is not sufficient to break the bonds holding surrounding particles, the expansion will probably damage the bonds associated with the surface of the starch grains which would represent a smaller disruption of the tablet matrix. Various figures have been put forward for the amount of swelling shown by starches on hydration, with Carmella et al. (1984) suggesting 43% and Gissinger and Stamm (1980) 103%, both for maize starch. However these figures were derived by different techniques and the relevance of the application of these figures to the expansion of starch in a particular compact is uncertain. The expansion in a compact will be constrained by the bonding forces between the starch and the surrounding particles and by the forces holding the surrounding particles in position around the starch. Thus expansions measured on single starch grains, i.e. unconstrained, should represent the maximal expansion whereas expansions measured in pure starch compacts represent an intermediate state depending on the strength of bonding and the packing of the starch grains. A more suitable quantity may be the

force developed during expansion, though this would only be useful where information is available on the bonding forces of the surrounding particles.

The main actions of starch in a tablet formulation are its action as a disintegrant or as a binding agent. The aim, as far as drug dissolution is concerned, being to disrupt the tablet structure and facilitate liquid access to the drug. The effect of changing the starch concentration on the rate of liquid penetration was insignificant (Table 5.5) and has already been discussed. Disintegration in a disintegration apparatus occurred too erratically to adequately distinguish between the different batches and little difference was shown in the time before the onset of dissolution in Figures 3.10 to 3.17. Thus the shorter T90% attributable to the increase in starch concentration was not adequately explained by a more rapid disintegration of the tablets.

The modification of a hydrophobic drug surface by starch has been discussed in Section 4.7, where the change in the ratio of starch to drug surface area was found to be similar to the time for 90% drug dissolution for the four combinations of drug particle size and starch concentration. A similar action may occur with the aspirin, which has a lower adhesion tension (Table 1.4) than the paracetamol previously discussed, and may therefore be expected to be more resistant to aqueous wetting (Fell and Efentakis 1978). The action of starch may therefore depend on the starch in contact with the drug surface rendering the contact point hydrophilic, the wetting then proceeding less rapidly than the rate of solution. This would account for the shorter T90% with a longer mixing time or a higher starch

concentration and indicates that the disintegration induced by the starch swelling was of less importance, otherwise the purely mechanical separation of particles would give a T90% dependent mainly on drug surface area.

The surface modification mechanism may have been supported by the effect of increasing the mixing time (Table 5.6b), where a longer mixing time would increase the distribution of starch and hence the number of starch grains in contact with the aspirin crystal surface, thus increasing the dissolution rate. However, increasing the mixing time also decreased the tablet tensile fracture stress (Table 5.3a) and decreased the time for 50% liquid penetration (Table 5.5a), either of which could influence the deaggregation of the compact and hence the dissolution process.

The interaction between starch concentration and mixing time was significant and is shown in Table 5.6d. It can be seen that the main feature of this table is the high T90% associated with the lower starch concentration and the shorter mixing time. This indicates that a critical level of starch distributed throughout the tablet was necessary for a rapid dissolution rate. This critical level may arise through either distribution of a low amount of starch or by the presence of a high amount of starch. It was not significantly increased by an increased distribution of a high amount of starch. The shorter T90% may represent the dissolution of the drug crystals themselves i.e. an intrinsic dissolution rate, and the longer T90% would represent the effect of the processes affecting the transport of liquid to and from the drug crystals. The liquid uptake into the tablet (Table 5.5c), was significantly slower with the low

starch, short mixing time combination. It was interesting that the increased distribution of magnesium stearate apparently failed to significantly lengthen the T90%, even at lower starch concentrations (Table 5.6d).

An increase in the compaction pressure resulted in a longer T90% (Table 5.6c), though at a relatively low level of significance. The interactions of starch concentration (Table 5.6e) and mixing time (Table 5.6f) with compaction pressure clarify the situation. These interactions are best discussed with reference to Table 5.6g which, despite being of a lower significance (Table 5.6) than the individual interactions, shows the elements of both. Table 5.6g may be split into two parts, the values associated with a short mixing time and a low starch concentration, and the remainder of the values. The significance of the interactions involving compaction pressure arises from the lower T90% attributed to a compaction pressure of $100MNm^{-2}$. The effect being masked by either a high starch concentration or a long mixing time. This was probably due to the strength of the tablet which was much weaker either as a lower tensile fracture stress (Table 5.3c) or as a higher friability (Table 5.4c), at the lowest compaction pressure compared to the two higher pressures. The liquid uptake was also more rapid at the lowest compaction pressure (Table 5.5d).

The dissolution process in these aspirin tablets may be summarised as depending mainly on the starch concentration which increased the dissolution rate up to the limit where the solution of isolated drug crystals became predominant, by some combination of its reduction in tablet strength, its disintegration of the tablet, and by its surface interaction with the drug. These

effects were enhanced by an increased distribution of the starch by a longer mixing time and were not affected by the magnesium stearate, the latter probably because the drug surface was initially hydrophobic. Under the conditions of low starch concentration and a short mixing time, the strength of the tablet became more important in controlling the dissolution process by promoting faster liquid ingress and facilitating disruption of the tablet structure.

5.8 A Summary of the effects of the Treatments on Aspirin Tablets.

This section summarises the foregoing discussion from a slightly different viewpoint, that of the treatment rather than the determinant.

5.8.1 The effect of altering the mixing time.

A longer mixing time reduced the tensile fracture stress, the M50% and the T90% of the aspirin tablets. It increased the tablet porosity and friability. The result of extending the mixing time will be a greater distribution of magnesium stearate over the surface of the particles in the formulation and a more homogenous distribution of the drug and excipients. Magnesium stearate has been shown to reduce bonding between particles on compaction where brittle fracture is not the main bonding mechanism (Lerk et al. 1979). This explains the reduction in tablet strength as shown by a lower tensile fracture stress and a greater friability (Tables 5.3a and 5.4a), and the increase in porosity (Table 5.2b); the elastic recovery of the particles permitted by the decrease in bonding increasing the void space. The reduction in M50% and T90% with a longer mixing time represents a faster rate of liquid uptake and a faster dissolution rate. This was surprising as the additional distribution of hydrophobic lubricant might be expected to retard liquid penetration and drug release. The increase in the rate of penetration may therefore have been due to the reduction in bonding which implies that the liquid entered via the capillary network between particles rather than through the

excipients. The rate of dissolution of the drug may have been dependent on the rate of liquid penetration. The shorter M50% with a longer mixing time would thus account for the more rapid T90%. However the most significant effect on the M50% was the mixing time but the changing the starch concentration was the most significant effect on the T90%. Thus although the rate of liquid penetration may have exerted a great influence on the dissolution rate, it did not entirely control it. An increased distribution of starch would occur with a longer mixing time. This would bring more starch into contact with the drug surface enhancing the wetting rate and thus the dissolution rate. It may also have reduced the M50%, the starch swelling on hydration sufficiently to disrupt the hydrophobic coating and providing a route for liquid ingress through the starch.

5.8.2 The effect of changing the starch concentration.

The effect of increasing the starch concentration in the formulation was similar to the effect of increasing the mixing time in that it reduced the tensile fracture stress, the M50%, and the T90%. It did not significantly affect the tablet porosity but increased the friability. The increase in starch concentration was accomplished by replacing Avicel with starch in the formulation. The mean diameter of the starch was greater than the Avicel it replaced as determined by a permeability method (Table 3.2). The total surface area in a given weight of powder was therefore lower with the high starch concentration than with a low starch concentration. The similarity with the effects due to a longer mixing time may thus be accounted for by an increase in the magnesium stearate per unit area with a concommitant

reduction in bond strength. The greater friability and the lower tensile fracture stress thus follow the same reasoning as with the mixing time, which may be extended to include the M50%. The lack of effect on porosity suggests that any elastic recovery of the starch was insignificant compared to the Avicel it replaced in the formulation. The effect of increasing the starch concentration on the dissolution rate (T90%) was more complex. Simple swelling of the starch grains promoting disintegration of the tablet was the most obvious mechanism. This did not seem likely as 50% saturation of the tablet occurred within 74 seconds whereas 50% of the drug appeared in solution in 21 minutes (Grand Means from Tables 5.5 and 5.7). This implies that the dissolution was not controlled by the rate of liquid penetration into the tablet, which would include the tablet strength effects. The main action of the starch therefore probably lies in the modification of the drug surface. The contact between starch and drug has been postulated to overcome the hydrophobic barrier of the aspirin surface and so permit wetting and hence dissolution to take place. This would account for the shorter T90% with a longer mixing time at the lower level of starch, and the lack of effect of a longer mixing time at the higher starch concentration (Table 5.6d).

5.8.3 The effect of changing the compaction pressure.

A higher compaction pressure increased the tablet strength as shown by the higher tensile fracture stress and the lower friability. The porosity was reduced under the same conditions. These all represent an increase in bond formation during more intimate particle contact

under the higher pressures. The effect of increasing the pressure from $100MNm^{-2}$ to $150MNm^{-2}$ was greater than from $150MNm^{-2}$ to $200MNm^{-2}$. This probably indicated that the maximum amount of bond formation had taken place at some pressure above $100MNm^{-2}$, thereafter the energy delivered by increased pressure was stored as elastic deformation. This would occur when sufficient consolidation of the particles or compact had taken place to allow the transmission of the compaction force to the die wall. The removal of the compressive force then allows the elastic recovery of the die wall to exert radial forces on the compact. This in turn breaks some of the bonds formed at the peak of compaction. In its worst case this may cause lamination of the tablet, but this was not apparent in these tablets. However it will cause a reduction in the tablet strength with a limiting value where the extra bonds formed on compaction are balanced by the residual die wall forces. There may have been some storage of elastic energy by some of the particles due to the uneven distribution of pressures within the compact with the same effect as energy stored in the die wall. The increase in strength with compaction pressure had comparatively little effect on the liquid uptake (M50%) or drug release (T90%). Both times were increased in a similar manner to the tensile fracture stress i.e. greater from $100MNm^{-2}$ to $150MNm^{-2}$ than above. The effect of compaction pressure on the T90% was more significant in the interactions with the starch concentration and mixing time (Tables 5.6e and 5.6f) than as a single treatment. In these the pressure could be seen to have an effect with the short mixing time or the lower starch concentration, but an increase in mixing time or starch concentration masked the effect.

CHAPTER 6.

A COMPARISON OF THE CHARACTERISTICS OF ASPIRIN AND PARACETAMOL TABLETS.

6.1 Introduction.

The effect of various treatments on the characteristics of aspirin or paracetamol tablets have been individually discussed in the preceding chapters. This chapter compares and contrasts the mechanisms involved and highlights the scope for further study.

The statistical design used for the experiments on the individual drugs could have been combined with the inclusion of the additional treatment of 'drug type', and the particle size analysed as a qualitative treatment e.g. small and large. However, the mechanisms influencing the determinants have been directly compared, rather than attempting to combine the analyses. A summary of general effects of the single significant treatments is presented in Table 6.1, this is a compilation from results presented in some of the preceding tables, the individual tables being referenced in the text.

Table 6.2 shows some of the characteristics of the two drugs which may have contributed to any differences observed.

An increase in:	Mixing Time	Starch Concentration	Particle Size	Compaction Pressure 100-150	Compaction Pressure 150-200 MNm^{-2}	
Effect on:						
Weight coefficient of variation.	0 -	0 0	0 -	0 0	0 0	aspirin paracetamol
Porosity.	+ +	0 +	0 -	- -	- -	aspirin paracetamol
Tensile Fracture Stress.	-- --	- -	0 -	++ ++	+ +	aspirin paracetamol
Liquid Uptake (M50%).	- +	- 0	0 +	+ +	+ 0	aspirin paracetamol
Dissolution (T90%).	- 0	-- --	0 -	+ 0	0 0	aspirin paracetamol

key: -- decreasing, - insignificant effect on the response, 0, + increasing, ++

Table 6.1.

A summary of the effect of an increase in a treatment on the tablet parameters.

Table 6.2

The Properties of aspirin and paracetamol.

	Paracetamol	Aspirin	Notes
Particle Size	7	328	A
(μm)	20	403	A
Particle Density (gcm^{-3})	1.29	1.35	B
Crystal Crushing Strength (MNm^{-2})	4.01	5.38	C
Solubility in:			
Water	1 in 70	1 in 300	D
Ether	insoluble	1 in 20	D
Adhesion Tension (Nm^{-1})	30.7	21.4	E
pKa (25°C)	9.5	3.5	F
Melting Point (°C)	169-172	135-143	D

Notes

A. Table 3.2; Section 2.2

B. Table 2.3

C. Markova and Balabudkin (1979)

D. B.P. (1980)

E. Table 1.4

F. Martindale (1982)

6.2 Tablet Weight Variation and Porosity.

The mean coefficient of tablet weight variation and the mean porosity of aspirin tablets were both less than those of paracetamol tablets, (Grand Means Tables 4.2, 4.3, 5.1 and 5.2). This follows the trend relating to the drug particle size shown in the paracetamol tablets, that is, as the drug size increased the tablet weight variation and porosity decreased, (Tables 4.2a and 4.3c). This was almost certainly due to a mass flow phenomenon, whereby the presence of larger particles carried small particles into the die and provided an initial consolidation of the powder bed, the larger the particles, the greater the effect within the range examined. Conversely this may be viewed as smaller particles causing uneven flow and interfering in consolidation. Danish and Parrott (1971) and Jones and Pilpel (1966) also found that smaller particles tend to limit flow.

Increasing the compaction pressure resulted in a reduction in tablet porosity, though over different ranges for the two drugs, (Tables 4.3a and 5.2a). This difference in range illustrates the importance of the initial consolidation in the die; with a more efficient die packing a smaller proportion of the energy delivered during compaction would be used in particle rearrangement. In the case of the smaller drug particles the rearrangement probably consisted of the breakdown of electrostatic bridging structures. Thus, as the compaction pressure increased, more particles were moved to a position where bond formation could take place. In this context it is interesting to note that the Grand Mean tensile fracture stresses for both drugs were

almost the same (Tables 4.4 and 5.3), despite the smaller surface area available for bonding with the larger aspirin crystals. This may indicate that an equivalent amount of the energy delivered during compaction was used in the paracetamol formulations for particle rearrangement and in the aspirin formulations for increased bonding. Both drugs exhibited the same changes with respect to the compaction pressure, i.e. a greater decrease in porosity between $100MNm^{-2}$ and $150MNm^{-2}$ than between $150MNm^{-2}$ and $200MNm^{-2}$, (Tables 4.3a and 5.2a). This probably reflected a change in the balance of forces within the compact after compression such that, when the pressure on the compact was released, then elastic recovery could take place. The non-linear decrease in porosity indicates that a limiting degree of bonding took place such that further increases in pressure did not result in a proportional increase in permanent bonds.

The effect of a longer mixing time was an increase in the tablet porosity with both drugs, although the change was slightly greater in the aspirin formulations, (Tables 4.3d and 5.2b). This was due to the effect of magnesium stearate on bond formation, a more complete distribution of the lubricant preventing some bonding from taking place. Any elastic recovery is then restrained by comparatively fewer bonds resulting in still greater disruption of bonding, the overall effect being an increase in porosity. The ratio of lubricant weight to unit particle surface area was greater in the aspirin formulations because of the larger drug size. This probably accounted for the larger change in porosity in these formulations. The coefficient of weight variation was unchanged by extending the mixing time in aspirin tablets, but was reduced in the

paracetamol tablets. This illustrates the action of magnesium stearate as a lubricant, rather than as an anti-bonding agent, although these actions are more a question of degree than true distinctions. The lubricant action may be ascribed to effects on temporary bonds or binding, that is those bonds which are easily broken, as distinct from less easily broken or permanent bonds. In the paracetamol formulations the temporary bonding took place through the electrostatic attraction between particles. An increased distribution of lubricant dissipated the charge thus increasing the consistency of powder flow and packing efficiency in the die, leading to a reduction in tablet porosity. The difference in drug particle size probably meant that electrostatic attraction was less influential in the aspirin formulations than with the paracetamol. The effect of increasing the mixing time was therefore due to the action of magnesium stearate in reducing permanent bonding in the aspirin tablets whilst this action in the paracetamol tablets was countered by a reduction in porosity as a result of the dissipation of electrostatic charges.

The effect of increasing the starch concentration was an increase in the porosity of paracetamol tablets but it had no significant effect on aspirin tablets, (Tables 4.3b and 5.2). This suggests that, in the aspirin tablets, any elastic recovery attributable to an increased starch concentration was constrained by the permanent bonds formed on compaction. The greater initial consolidation during die filling with the aspirin resulting in a more rigid tablet structure capable of resisting a greater amount of elastic recovery stress than the paracetamol tablets. The energy

involved however, meant that the aspirin tablets were to some extent prestressed. There may have been some effect of the decrease in specific surface area of the powders at the higher starch concentrations, resulting in an increase in the weight of lubricant per unit particle surface area. This was unlikely to account for any difference between the two drug formulations as the size difference between the drugs was greater than between the starch and the Avicel it replaced. It should also be noted that there may have been a contribution to the lower mean porosity of the aspirin tablets from the porosity of the drug crystals themselves.

6.3 Tablet Strength.

Although the previous chapters have considered tablet strength in terms of tensile fracture stress or friability, the relationship shown in Figure 6.1 is such that a consideration of the tensile fracture stress alone is sufficient to compare the aspirin and paracetamol formulations.

The strengths of aspirin and paracetamol tablets were similar with all of the treatments except for the drug particle size. The mixing time had the greatest effect on the tablet strength, a longer time reducing the strength, (Tables 4.4a and 5.3a). This was almost certainly due to an increased distribution of magnesium stearate preventing bond formation during compression.

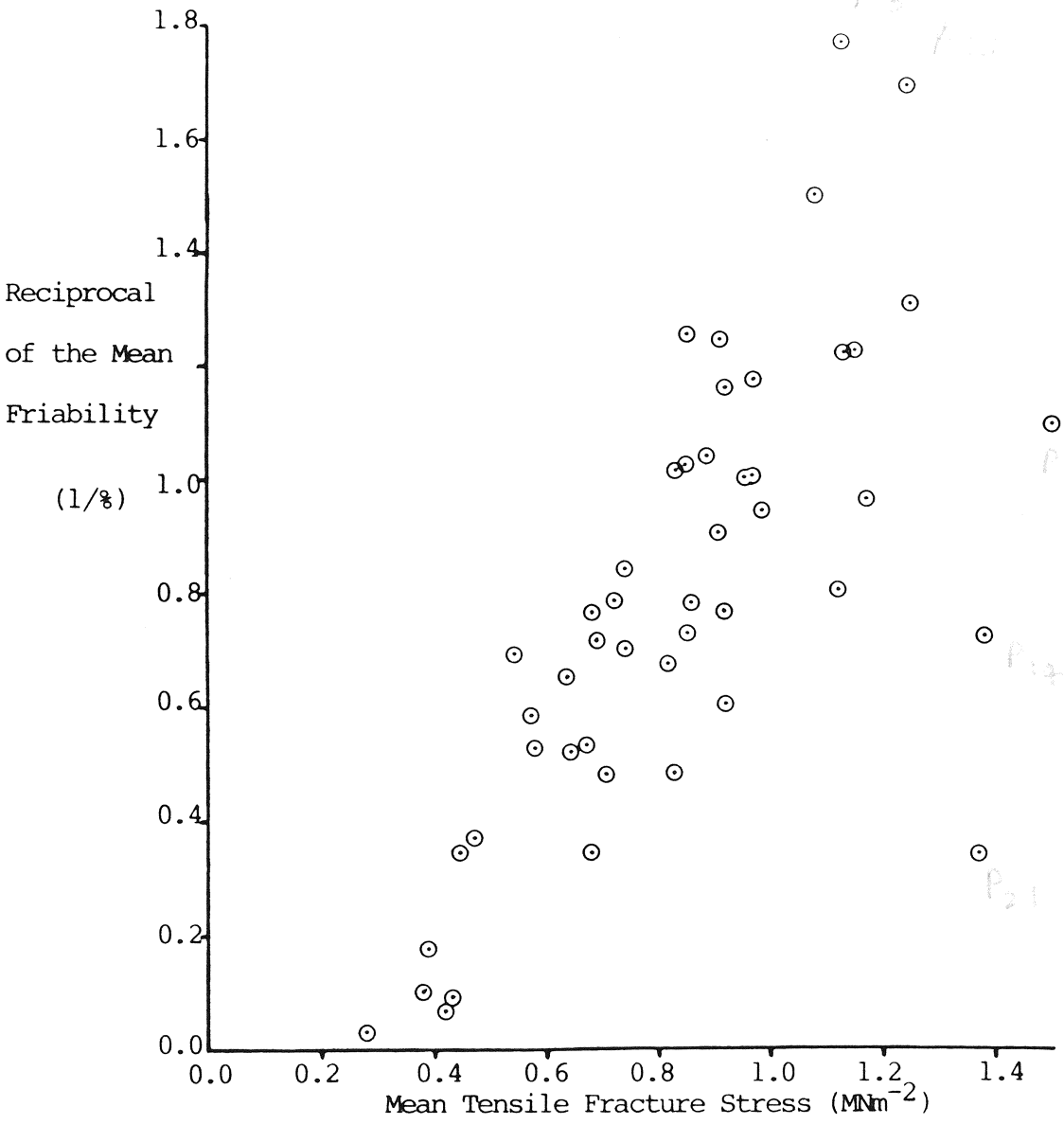

Figure 6.1

The relationship between the mean tensile fracture stress and the reciprocal of the percentage friability for aspirin and paracetamol tablets.

An increase in the starch concentration resulted in a decrease in the tablet strength, (Tables 4.4b and 5.3b). This effect has been postulated to depend on two different factors; the larger size of the starch compared to the Avicel it replaced in the formulation and the intrinsic properties of the starch. The greater surface-volume diameter of the starch (Table 3.2) would result in an increase in the magnesium stearate available to interfere in bonding and a reduction in the area available for bonding. Starch may also act as a 'weak link' in the tablet structure, due either to the stresses imposed by the elastic recovery of the starch or by a reduced ability of the starch to bond (i.e. weaker starch-Avicel bonds compared to Avicel-Avicel bonds).

An increase in the compaction pressure caused the particles in both drug formulations to move closer together with a resultant increase in bonding and tablet strength, (Tables 4.4d and 5.3c). The increase in strength was non-linear, indicating that the bonds formed during compression were becoming balanced by the increasing forces of elastic recovery.

The Grand Mean tensile fracture stress for both drugs were almost the same, (Tables 4.4 and 5.3). This suggests that the principal bonding occurred without reference to the drug. This probably represented drug particles embedded in an Avicel matrix.

6.4 Liquid Penetration.

The time taken to attain 50% saturation of a tablet, (M50%), using water containing a radiotracer, has been used as a measure of the rate of liquid penetration. A longer M50% thus represented a slower rate of penetration.

The liquid penetration into aspirin tablets appears to have been dependent on the tablet strength, (Figure 5.1). The stronger the tablets the longer the M50%. One consequence of this was that the M50% ANOVA was similar to that of the tensile fracture stress, (Tables 5.5 and 5.3). The mixing time was therefore the most significant treatment affecting the M50% of the aspirin tablets. The mixing time also had a significant effect on the M50% of the paracetamol tablets. In the aspirin tablets a longer mixing time decreased the M50% whereas in the paracetamol tablets the M50% was increased, (Tables 4.6a and 5.5a). The predominant effect of an increased distribution of magnesium stearate on the M50% of the paracetamol tablets was to render more surfaces hydrophobic, thus retarding liquid uptake. The interference in bond formation by the magnesium stearate exerted the main effect on the M50% of the aspirin tablets. It has already been noted (Section 6.3) that the reduction in the strength of both aspirin and paracetamol on increasing the mixing time, was similar. This suggests that the particle surfaces were the main barriers to penetration, either the interface between the hydrophilic excipients and a void space, or another hydrophobic surface. The latter including a drug surface or a coating of magnesium stearate. With the shorter mixing time, a similar comparison may be made between

the two drugs as between the two size fractions of paracetamol. That is, the mechanism controlling the penetration was the path length required to bypass a drug crystal, the larger the hydrophobic crystal, the greater the path length deviation and the longer the M50%. When the mixing time was increased, the distribution of magnesium stearate was increased whilst the strength decreased. A reduction in the tensile fracture stress allowed the Avicel to split apart on hydration more easily owing to a reduction in the number of restraining bonds. This effect was opposed by the increase in hydrophobic surface as a consequence of the increased magnesium stearate distribution. An illustration of the effect of the spreading of an additional hydrophobic coating may be obtained by considering a uniform 1μm layer of lubricant deposited on two different spheres. The diameter of a 10μm sphere is then increased to 12μm whereas a 350μm sphere is increased to 352μm. The relative increases are thus 20% and 0.6%. The effect of a longer mixing time on the M50% in aspirin tablets therefore represents the lack of restraint to Avicel splitting apart on hydration. In the paracetamol tablets this action probably had a similar effect but was overshadowed by the additional hydrophobic barrier of the lubricant.

Increasing the starch concentration had no significant effect on the paracetamol tablets but resulted in a shorter M50% in the aspirin tablets, (Tables 4.6 and 5.5b). The same arguments relating to the effect of the mixing time on the M50% also apply to the effect of starch in the formulations. An increase in the starch concentration has been shown to reduce the tensile fracture stress of tablets containing either drug. The M50% might therefore be expected to fall, as happened in

the aspirin tablets. The porosity of paracetamol tablets was greater than that of the aspirin tablets, which meant that there was a less continuous matrix for penetrating liquid to follow. The reduction in strength with a higher starch concentration was therefore less effective than the lack of matrix continuity in the penetration of liquid into the paracetamol tablets.

Raising the compaction pressure resulted in a longer M50% for both drugs, (Tables 4.6c and 5.5d). The M50% of the aspirin tablets again followed the tensile fracture stress with a greater increase between the lower pressures than the higher. The increase in M50% in the paracetamol tablets was similar to the aspirin tablets between $100MNm^{-2}$ and $150MNm^{-2}$. Between $150MNm^{-2}$ and $200MNm^{-2}$ the increase in the M50% of paracetamol tablets was greater than that of the aspirin. This simply reflects the change in tablet strength with both drugs, (Tables 4.4d and 5.3c).

6.5 The Dissolution Rate.

The time for 90% of the drug to be released (T90%), has been used to represent the drug dissolution rate. A longer T90% thus represented a slower rate of drug release from the tablet.

The only treatment which had a significant effect on the T90% of both the aspirin and paracetamol tablets was the starch concentration, (Tables 4.7 and 5.6). In both cases the T90% was reduced by a similar time when the

starch level was raised, (Tables 4.7a and 5.6a). The usual explanation for a more rapid drug dissolution in the presence of a higher disintegrant concentration is that the drug particles in a tablet are more efficiently seperated allowing access of the solvent to the drug. In a directly compressed tablet, i.e. a tablet not formed from a prior granulation process, disintegration is largely confined to the initial stages of a dissolution test. This manifests itself as a plateau or low gradient slope at the start of a profile of the percent dissolved against time. In the tablets examined in this study there was little to distinguish the tablets containing a higher starch concentration from a lower concentration with regard to this initial phase of dissolution, (Figures 3.2 to 3.17, batches 7-12 and 19-24 contain more starch). The porosity of the tablets was such that a volume expansion of the starch grains may have been absorbed by the available void space within the tablets. The dissolution profiles and the porosity suggest therefore that the disintegrant action of starch was unlikely to account for the shorter T90% with a greater concentration of starch in the tablet. The surface interaction between the starch and the drug has therefore been postulated to account for the action of starch in these tablets. The most striking example of the similarity between the ratio of starch to drug surface area and the T90% is shown in Table 4.10. It has been suggested that the starch acts as a bridge, for the solvent, over the hydrophobic barrier of the drug surface. Undoubtedly there will be an element of the volume expansion of starch breaking up the tablet structure and perhaps the inability of starch to bond to other surfaces (Hess 1978) but not as mechanisms which controlled the dissolution rate.

A change in the mixing time had a significant effect only in the aspirin formulations, (Tables 4.7 and 5.6). A longer mixing time resulting in a shorter T90% i.e. a more rapid dissolution rate, (Table 5.6b). Likewise the effect of a greater compaction pressure produced a significant increase in the T90% of aspirin tablets but not in paracetamol tablets, (Tables 4.7, 5.6 and 5.6c). Both of these treatments were probably dependent on the rate of liquid penetration and therefore (Section 6.4) on the tablet strength. If the starch/drug interface is considered to act as the controlling mechanism for the wetting of the drug and the initiation of dissolution, then the rate at which the solvent reaches the starch becomes a necessary first step. The M50% in the aspirin tablets was shorter than that in the paracetamol tablets, (Grand Means Tables 4.6 and 5.5), and related to the tensile fracture stress, (Figure 5.1). It was probably the latter relationship which caused the effect on the T90% of the aspirin tablets. A longer mixing time reducing the tensile fracture stress, leading to a more rapid liquid ingress and thus a shorter T90%. Similarly with the compaction pressure, a higher pressure produced stronger tablets which were not penetrated as easily by the liquid, leading to a slower rate of dissolution. In the paracetamol tablets these effects were masked by the slower penetration rate and the smaller size of the drug particles. The dissolution of the drug on the outside of the tablet possibly taking place well before the solvent had fully penetrated the tablet.

6.6 Conclusions.

The quantitative prediction of tablet parameters has not been attempted in this study. The reason for this omission was that the effect of a given change on a tablet depends on the mechanisms acting under a particular set of conditions. Equations relating the various treatments would be inapplicable even with small changes in the formulation whereas those changes might only influence the relative dominance of the underlying mechanisms. The variation in dominant action was especially noticable with the distribution of magnesium stearate during prolonged mixing, when the effective mechanisms may have been a reduction in bond strength, a reduction in electrostatic particle interactions or an increase in surface hydrophobicity. Thus, in the presence of large, hydrophobic particles the dominant mechanism was that of a reduction in bonding. Where smaller, electrostatic particles were present, the interference in bonding was offset by an increase in particle surface, the net result being tablets of similar strength. The difference in the balance of mechanisms led to different effects when there was a tablet/liquid interface. With larger drug crystals liquid penetration depended on the tablet strength but with the smaller drug particles penetration depended more on the additional hydrophobic component of the lubricant than its effect on strength. This balance in mechanisms carried through to the effects of mixing on the T90% although this was much less important than the effect of increasing the starch concentration. Thus, the mixing time only had a significant effect on the T90% in the aspirin tablets where the tablet strength was reduced but with little additional hydrophobic effect.

Starch levels had a similar effect in both aspirin and paracetamol tablets. An increase produced its most pronounced effect on the T90%, but also had minor effects on the tablet strength. The T90% and tensile fracture stress were both reduced, the latter as a result of the difference in compression characteristics between the starch and Avicel. A novel mechanism has been proposed to account for the action of starch in drug dissolution. The surface interaction between starch and drug, whereby the starch acted as the initiator for wetting the drug crystals, offered a suitable explanation of the observed responses. more clearly in P

The effect of altering the drug particle size produced significant responses only within the paracetamol formulations where the relative difference in particle size was much greater than in the aspirin formulations. However some of the effects were continued as trends, i.e. no difference was observed within the aspirin formulations but the effect of larger drug particles was apparent in the sequence; small paracetamol < large paracetamol < aspirin. This was exemplified by the decrease in porosity and the coefficient of tablet weight variation with an increase in the drug particle size.

An increase in compaction pressure produced a greater effect between 100 and 150MNm^{-2} than between 150 and 200MNm^{-2} . This non-linear response was indicative of an incipient tendency to lamination, which became apparent in the friability testing of the paracetamol tablets, where some tablets broke apart during testing. There was a decrease in tablet porosity and an increase in strength and M50%, when the compaction pressure was raised. The T90% was not greatly affected by the

compaction pressure, the only change being shown between the two lower pressures in the aspirin formulations. The effect of increasing the compaction pressure was to increase particle proximity and therefore bonding. Hence, the tablet strength was increased and liquid penetration made more difficult, the latter arising from the lower porosity and a reduction in the ability of Avicel to split apart on hydration due to the more rigid tablet structure.

6.7 Further Work.

6.7.1 General Considerations.

The systems involved in producing a biologically effective tablet are known to be a complex set of interacting variables. This study has been addressed to a small subset of those variables. One major area which has been omitted is the extension to in vivo studies. Indeed, the application of a factorially designed experiment concentrated on biological and tablet manufacturing variables may provide some insight into the problem of in vitro/in vivo assessment of any dosage form.

There are many facets of the present work which would merit further examination. One of the most obvious would be an expansion of the levels, and possibly the number, of treatments which would enable predictive formulae to be established. This could be either as polynomial expressions relating the treatments to the response, or as response surface maps.

The main result of this work has been to explore the mechanisms influencing a direct compression formulation, and, more importantly, the effective balance of those mechanisms on measurable tablet characteristics. The first step was the establishment of modes of action in simple model systems. Thus, the spreading of magnesium stearate during mixing has been examined by Lerk et al. (1982) and others, the response of Avicel to hydration has been examined by Fukuoka et al. (1983) and dissolution theories derived by Nernst and Brunner (1904). Most of the mechanisms invoked here were based

on past work. The approach adopted here however, represents the second step, that is the interaction of those mechanisms in a tablet. The final step would be an understanding of the factors influencing the relative balance of the basic mechanisms. For this to be achieved, and therefore to predict tablet charact--eristics from a knowledge of the materials and their processing, a much wider base is required of 'balance of mechanisms' data than is presented here. The detailed considerations in the following section cover some of the work which would be necessary to extend this database, as well as filling some of the gaps in understanding the basic mechanisms.

6.7.2 Detailed Considerations.

Starch, in one form or another, is the most widely used tablet disintegrant. It is therefore surprising that its mode of action has not yet been completely elucidated. In this study a novel mechanism has been proposed whereby the action of starch as a disintegrating agent is considered as a subsidiary factor to its ability to promote wetting of the drug crystals. Undoubtedly this proposition requires further scrutiny. A clear distinction might be expected between wet granulated tablets, (where starch may be used as a binder and a disintegrant), and directly compressed tablets, (where the binding properties tend to be less important).

The role of disintegration as a precurser to dissolution has largely been circumvented in this study by considering the dissolution and the liquid penetration. There remains an element of doubt as to the action of

starch in the tablets. Unfortunately an adequate representation of a given batch of tablets could not be made using standard tests. Thus, although it has been shown that a disintegration test does not necessarily provide an indicator of the rate of dissolution of a drug, it may equally be argued that a dissolution test does not adequately predict in vivo absorption. With suitable modification, as in a dissolution test, it may be possible to use a disintegration test to predict the in vivo behaviour of a dosage form. This might be expected to be more fruitful when applied to less homogenous tablets, i.e. those made from granules rather than tablets based on a more homogenous matrix structure. A similar experimental design based on granulated tablets might therefore usefully employ a disintegration test, particularly if the level of discrimination in the test was similar to the granule size.

The measurement of tablet strength in this study has been concentrated on the tensile fracture stress and friability. It has also been found that the reciprocal of the friability mirrored the tensile fracture stress. The only problem occurred where tablets broke during the friability test. This has been taken, along with non-linear responses to an increased compaction pressure, to indicate that a degree of weakening of the tablet structure had taken place. Alternative measurements of tablet strength such as the work of failure, might provide a clearer insight into the relatively extreme state of incipient lamination, but require more sophisticated tablet machine instrument--ation than available in this study. Other indices such as the brittle fracture propensity (Hiestand et al 1977) might also be useful although a clarification of the

basic mechanisms involved in the strength and formation of bonds between particles under stress would be a great step forward in understanding the process of tabletting.

The structure of a tablet made by a granulation process will be different from a direct compression formulation. The manufacturing process, particularly in wet granulation, is much more complex, (Table 1.1). As many tablet formulations are still made by wet granulation, a rigorous examination of the variables involved by means of a similar experimental design to that employed here would be useful in formulation design. The granulation process would be an obvious starting point, although, to keep the scope of the experiment within bounds, the characteristics of the granules might be a more feasible approach. This might include such factors as the granule strength and size distribution, as well as its constituents. A division of the experiment into those factors affecting the characteristics of granules and those parameters of the granule which influenced tabletting, would provide an alternative approach.

A novel method of assessing liquid penetration into tablets has been used in this study, (Section 2.8). This is an important area in understanding the dissolution of tablets, as it is the first step in bringing a solvent into contact with a drug particle in a tablet. Admittedly the relevence of liquid penetration is restricted to those tablets which are not 'blown apart' by the inclusion of 'super' disintegrants, but where liquid ingress is restricted, even these disintegrants may be inhibited. The rate of

liquid penetration has been examined by several authors such as Buckton and Newton (1985) and Lerk et al. (1979) but there remains scope for further study particularly in the area of penetration in cases where the surface energy has been altered e.g. by the presence of other ingredients or by mechanical processes. The situation is complicated by the response of excipients to hydration. Simple capillary models have been shown to break down when pore sizes change during hydration, (Fukuoka et al. 1983). An examination of the liquid uptake characteristics of a range of tablet formulations, in terms of both the rate and extent of penetration would therefore provide a basis for considering the dissolution of drugs in tablets which do not follow the classical dissolution theories.

The effects of the mixing process on tablets has been closely examined in this study using in particular, the well established assumption that surfaces were coated with magnesium stearate with a longer mixing time. Whilst this was undoubtedly the major action of an increase in mixing, the effect on the interaction of other excipients has been neglected. Mixing is a fundamental pharmaceutical process which deserves further attention. It would be especially useful if firm correlations could be established between the various mixers, obviously with due consideration to the materials being processed. More generally, the mechanics of powder interactions, either as loosely joined or as bonded agglomerates, remains poorly understood.

The use of other excipients in a study of this type might be expected to show considerable differences in tablet characteristics. For example substituting the Avicel for an excipient which bonds with brittle

fracture, (such as dicalcium phospate), would reduce the effects of lubricant spreading. A non-shearing lubricant, (such as PTFE), might assist in understanding the mechanisms of lubricant action within the formulation. Changes in the formulation, the drug or the proportions of the ingredients would all contribute to a knowledge of the relative importance of the balance between the basic mechanisms.

There will be a contribution in any experiment from the equipment and test methods employed. The USP dissolution test is known to be susceptible to variations in apparatus (Cox et al. 1982). Changes in the operating conditions, such as the stirring speed, also influence the measured rate of dissolution from a tablet. Alternative testing methods may result in equally strong influences. The problem with dissolution testing is that of conflicting aims. It is a means of modelling the release of a drug from a dosage form and a means of assessing the initial in vivo behaviour of the dosage form. These aims are compatible only when a strong in vitro / in vivo correlation has been established. It is from this point of view that the dissolution test should be examined, although this might conflict with the commercial development of a tablet. As with the mixing process it would be useful if correlations between different techniques and apparatus used for dissolution testing could be established. In this context the work of Grijseels (1981) on hydrodynamic conditions may represent one way forward.