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The effect of waxes, hydrolysed gelatin and moisture on the compression characteristics of paracetamol and phenacetin

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Stearic acid or hard paraffin added to crystals of paracetamol and phenacetin reduced capping of tablets prepared by direct compression but did not produce acceptable tablets because the inter-particular bonds were very weak. The pressure cycle that can be constructed from the measurement of the axial pressure and the corresponding die wall pressures offers information that is useful in the formulation of tablets. The behaviour of paracetamol or phenacetin and their mixtures with gelatin hydrolysate or water or both shows a similarity to a Mohr body and it appears that the maximum die wall pressure is affected by the particle size of the material compressed and also by the additives present. Good transmission of radial force implies that the material can be initially consolidated, but alone it does not indicate that the tablet formed is physically stable. When the tablet formed remains coherent after the axial pressure is removed the residual die wall pressure remains high. Measurement of the residual die wall pressure might therefore be a useful indicator for identifying satisfactory formulations of substances that cap readily. Hydrolysed gelatin or water or both together produced paracetamol and phenacetin mixtures with satisfactory compression characteristics.

Paracetamol and phenacetin are substances that give rise to tablets which are prone to capping. Elowe, Higuchi & Busse (1954) studied the compression behaviour of phenacetin granules containing a low proportion of partially hydrolysed starch and found the tablets capped at high compression forces. Leigh, Carless & Burt (1967) determining the pressure cycle for paracetamol containing 3% polyvinylpyrrolidone also found capping to occur. Burlinson (1968) pointed out that crystalline substances that capped readily, compressed better as powder. This is so with paracetamol and phenacetin. This work is concerned with the effect of gelatin hydrolysates and moisture on the compression characteristics of paracetamol and phenacetin and the value of the pressure cycle in the prediction of capping.

MATERIALS AND METHODS

The paracetamol and phenacetin B.P. were dried for 4 h at 60° before use and −40 +60 mesh (BSS) fractions separated. In addition a sample of each subtance was powdered in a ball mill, passed through an air-jet sieve and the mean particle size determined; this was 60 μm for paracetamol and 75 μm for phenacetin.

Stearic acid B.P.C., hard paraffin B.P., glass distilled water and two gelatin hydrolysates were used as additives. The gelatin hydrolysates were commercial samples, Byco A (LMW hydrolysate) (mol wt 1000–2000) and Byco C (HMW hydrolysate) (mol wt 10 000–12 000) supplied by Croda Food Products Ltd. Comparisons were made with a direct compression paracetamol (Graesser Salicylates Ltd) which is reputed to contain 4% of a gelatin hydrolysate.

The effect of the additives was studied on the −40 +60 mesh fractions of paracetamol and phenacetin.

Stearic acid, dissolved in chloroform, was added in small quantities to a sample of drug crystals in a rotating coating pan to give a concentration of 1% w/w of stearic acid after the solvent had been removed. Drug crystals coated with 1% hard paraffin were similarly prepared.

Water to give a 2% w/w content was added by spraying onto crystals of the substances being rotated in the pan. The uniform distribution of the water was checked by a thermogravimetric method (Rees, 1967), taking samples from different parts of the batch and assaying.

A sufficient quantity of the required type of gelatin hydrolysate powder to give 4% w/w concentration was added to the dry crystals and also to the wetted crystals in a cylindrical wide mouthed jar

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which was closed and placed on a roller mill for 1 h to mix. Each of these samples was compressed on a single punch compressing machine. The top and bottom punches were instrumented with strain gauges as described by Shotton & Ganderton (1960a) and the radial pressure measured by inserting a piezo-electric transducer (Kistler 601H) through the die wall.

Five tablets were prepared from each sample at machine settings which gave approximately 45, 90, 135 and 175 MN m^{-2} compaction pressures. The mass of material, calculated from the true density of the materials, was sufficient to give a cylindrical tablet of 4 mm length at zero porosity using a 12 mm diameter punch and die set. The punches and die were lubricated by applying a 2% solution of stearic acid in a mixture of equal parts acetone and carbon tetrachloride with a camel hair brush and allowing the solvent to evaporate. The punch tips and die were polished with metal polish and degreased with acetone after each compression. The crushing strength of the tablets was determined after 24 h using the diametral crushing test described by Shotton & Ganderton (1960b). To avoid evaporation the samples containing water were weighed and compressed immediately afterwards.

RESULTS AND DISCUSSION

Both the crystalline and powdered forms of paracetamol and phenacetin produced tablets which were mostly unsatisfactory because they were too soft or capped. Tablets from crystals coated with stearic acid or hard paraffin showed no sign of capping but crumbled easily after ejection because the bonding between crystals had been weakened. The reduction of capping was similar to that reported for hexamine by Shotton & Ganderton (1961) but with hexamine the tablets formed were strong enough to be measured by the crushing strength test. These authors considered the capping occurring at the stress loci due to the die wall pressure and the elastic axial recovery after removal of the axial pressure, was prevented by the presence of stearic acid. This probably weakened the bonding area and allowed elastic recovery to take place partially at the expense of the bond. With the paracetamol and phenacetin there would be a similar effect but an even weaker particle-particle bond.

The pressure cycle plots for the powdered phenacetin are shown in Fig. 1 and for paracetamol in Fig. 2. The pressure cycles for the −40 +60 mesh crystals and the 'direct compression' paracetamol

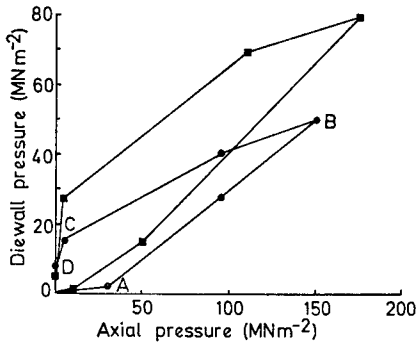

FIG. 1. Compression cycles for phenacetin. ● Crystals −40 + 60 mesh. ■ Powder d_m = 75 μm.

(Shotton & Obiorah, 1975) have been included for comparison.

The maximum die wall pressure was greater for the milled material than for the −40 +60 mesh material but the residual die wall pressure after removing the axial force was low when compared with the direct compression paracetamol powder and approximately the same in all cases.

Table 1 shows the slopes of the lines making up the different parts of the pressure cycle.

The initial slope, 0A, for an isotropic solid plug, is due to an elastic deformation and is given by $\nu/(1-\nu)$, where ν is the Poisson's ratio (Long, 1962). The tablet formed however was porous, even at the greatest loading used, and the slope of 0A will be different from that calculated from the Poisson's ratio. The direct compression paracetamol gives a greater initial transmission of force to the die wall but a lower maximum and a greater residual die wall pressure than with the pure powdered substance since separation (capping) did not occur.

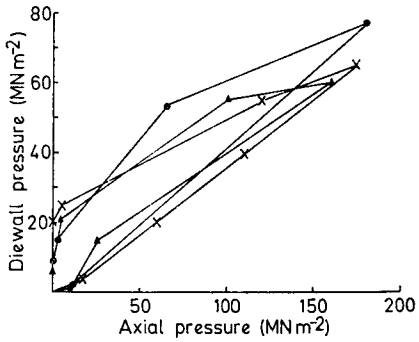

FIG. 2. Compression cycles for paracetamol. + direct compression paracetamol. ▲ crystals −40 + 60 mesh. ● powder d_m = 60 μm.

Table 1. *Slopes of different parts of compression cycles for phenacetin and paracetamol.*

Material	Mesh or Particle size	OA	AB	BC	CD
Phenacetin crystals	−40 + 60	0·14	0·40	0·24	1·50
Paracetamol crystals	−40 + 60	0·10	0·39	0·25	3·88
Phenacetin powder	75 μm	0·18	0·47	0·30	0·58
Paracetamol powder	60 μm	0·17	0·45	0·35	3·00
DCP powder	200 mesh	0·23	0·45	0·24	1·00

The addition of the LMW hydrolysate and water separately or together on the compression characteristics of the −40 +60 mesh paracetamol and phenacetin crystals gave tablets that were well formed and that showed no signs of capping. Lazarus & Lachman (1966) reported the surface of potassium chloride crystals to be altered by moisture due to surface dissolution and recrystallization on drying. This phenomenon may play but a small part in the improved consolidation of paracetamol and phenacetin crystals as the solubility is low. However, this may be sufficient to produce clean surfaces for bonding and surface tension forces will bring crystals into close proximity. In addition the liquid films act as a hydrodynamic lubricant (Rees, 1967) and this would facilitate consolidation.

The LMW hydrolysate added as a fine powder, acts as an adhesive to form stronger tablets and when water is also present, tablet strength is further improved as shown in Fig. 3, the swollen hydrolysate being spread more readily over the crystal surfaces.

The effect of these additives on the compression cycle of both paracetamol and phenacetin was similar. The maximum die wall pressure was increased regularly at each machine setting, Fig. 4, showing a moderate increase in force transmission in the order of 4% LMW hydrolysate +2% moisture >4% LMW hydrolysate >2% moisture. However, the tablet strength was more dramatically improved when the hydrolysate was present than with water alone. A closer parallel with tablet strength was found by comparison of residual die wall pressures which were much increased by the additives, in the same order as given above, Fig. 5.

The effect of the additives upon the pressure cycles is similar to that seen with the direct compression paracetamol. The overall shape of these curves approximates to that of a Mohr body. During the compression of a powder, stress concentrations occur at points and edges which could exceed the yield stress so that plastic deformation would occur, similar to microsquashing (Gregory, 1962). When the area increases materially and bonding occurs between the freshly exposed surfaces, elastic deformations followed by plastic flow will occur in the mass as a whole as the pressure increases. In the compression cycle, the yield point at A is unlikely to be sharply defined if readings are taken at small pressure intervals.

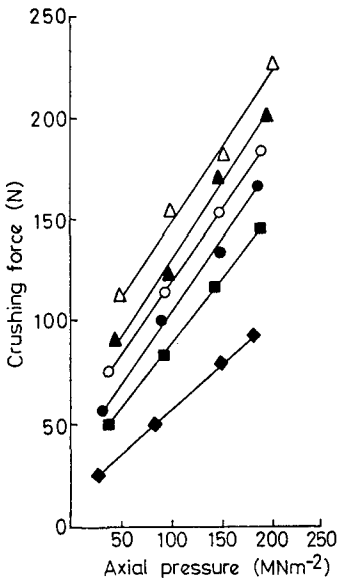

FIG. 3. The effect of additives on the crushing strength of tablets. △ Paracetamol with 4% LMW hydrolysate and 2% water, ▲ Paracetamol with 4% LMW hydrolysate. ■ Paracetamol with 2% water. ○ Phenacetin with 4% LMW hydrolysate and 2% water. ● Phenacetin with 4% LMW hydrolysate. ◆ Phenacetin with 2% water.

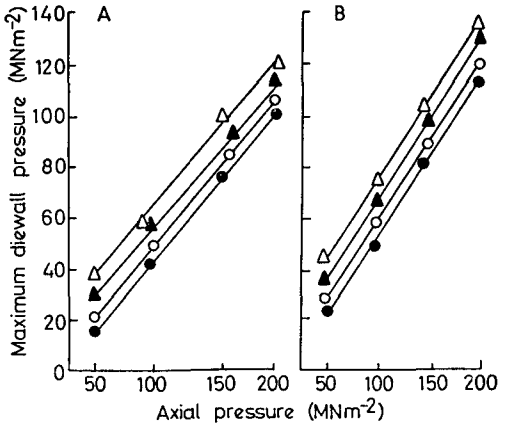

FIG. 4. The effect of additives on the maximum die wall pressure. A—Paracetamol, —40 + 60 crystals and B—phenacetin —40 + 60 crystals. ● alone. ○ with 2% water. ▲ with 4% LMW hydrolysate. △ with 4% LMW hydrolysate and 2% water.

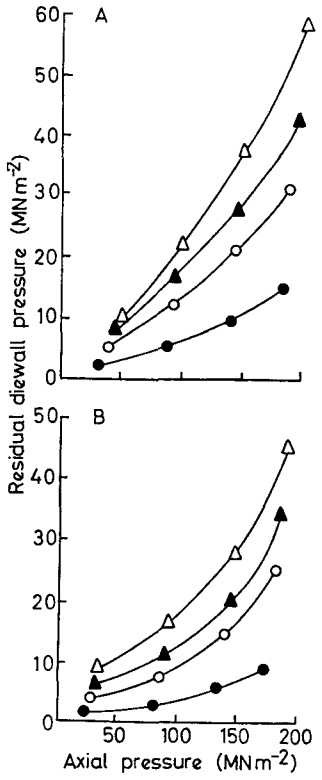

FIG. 5. The effect of additives on the residual die wall pressure when axial pressure is reduced to zero. A—Paracetamol —40 + 60 crystals and B—phenacetin —40 + 60 crystals. ● alone. ○ with 2% water. ▲ with 4% LMW hydrolysate. △ with 4% LMW hydrolysate and 2% water.

However, when the axial pressure is being relieved at B the recovery will be elastic at first and where failure occurs within the compact the pressure on the die wall falls rapidly as at CD, but the axial expansion applies pressure upon the punch face and then as the punch face moves away from the surface of the compact a very rapid fall in die wall pressure results as separation at the stress loci takes place. Separation will be accentuated if the movement of tablet is restricted by friction at the die wall. When moisture, gelatin hydrolysate or both are present, the compact is more strongly bonded and separation does not occur so that a greater die wall pressure results. In addition the additives appear to act as lubricants at the die wall as shown by the greater transmission of axial force to the lower punch (Table 2). Similar results were obtained when the higher molecular weight hydrolysate was used.Thus the residual die wall pressure appears to be an indicator showing whether capping will occur and could be useful in determining a preferred formulation.

Table 2. *Values of the applied pressure (P_A), bottom punch pressure (P_B) and punch force ratio ($R = P_B/P_A$).*

Material	P_A (N)	P_B (N)	R
Crystalline paracetamol —40 + 60			
Alone	16 012	12 878	0·804
+ stearic acid	15 406	13 739	0·892
+ hard paraffin	15 823	14 370	0·908
+ moisture 2%	15 537	14 148	0·911
+ LMW hydrol. 4%	16 524	15 395	0·932
+ moisture 2% + LMW hydrol. 4%	16 708	15 259	0·913
Crystalline phenacetin —40 + 60			
Alone	15 008	13 016	0·867
+ stearic acid	13 945	12 414	0·890
+ hard paraffin	14 421	13 178	0·914
+ moisture 2%	13 767	12 726	0·924
+ LMW hydrol. 4%	15 892	14 972	0·942
+ moisture 2% + LMW hydrol. 4%	16 349	15 224	0·931
Direct comp. paracetamol	17 505	16 024	0·915

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