The strength of tablets of mixed components

J. M. NEWTON*, DENISE T. COOK, CHRISTINE E. HOLLEBON, *Pharmacy Department, Nottingham University, Nottingham, U.K.*

The ability to predict the strength of a tablet of mixed components from the strength properties of the individual components, would be a great advantage in tablet formulation, especially using direct compression aids. Fell & Newton (1970b) were able to show this was possible for mixtures of various types of lactose of approximately the same particle size. When, however, the different forms of lactose were present in the same crystal, prepared either by spray drying or crystallization, the strength of the tablets, prepared by compaction of such crystals was not related to the composition of the mixture (Fell & Newton, 1971). The previous studies involved lactose that readily forms tablets. The present study investigates the extension of the concept of strength predictability to systems which contain a drug, phenacetin, which will not readily form tablets by compression, and a direct compression aid, dicalcium phosphate.

Dicalcium phosphate, not less than 98%, was obtained as Emcompress from Kingsley & Keith. The phenacetin was obtained from the Boots Company. The apparent particle densities (as determined by a liquid displacement) were 2·35 and 1·23 g cm^{-3} respectively. The mean surface area diameter (determined by Fisher sub-sieve analyser) was 52 μm for the dicalcium phosphate and 20 μm for phenacetin. Blends of known proportions by weight, were prepared by mixing and tumbling in glass bottles at 40 rev min^{-1} for 30 min. Magnesium stearate, 1% of superfine grade, Bush, Boake Allen Ltd., was added to the mixture before the blending process.

A constant weight of powder was compacted by flat faced punches within a 1·25 cm diameter die. Pressure was applied to the upper punch, via a proving ring, from a crosshead driven downwards by a lead screw mechanism which provided a controlled movement of 1 mm min^{-1}. The deformation of the powder bed was measured by a dial gauge micrometer. On reaching the required pressure the crosshead was reversed at the same speed. The compact was removed from the die by removing the lower punch and applying pressure from the upper punch, again at 1 mm min^{-1}, the force necessary to initiate ejection being recorded on the proving ring. The weight and dimensions of the compact were determined to $\pm$0·001 g and $\pm$0·05 mm respectively. The load necessary to cause tensile failure of the tablet was determined by the diametral compression test (Fell & Newton (1970a). The load was applied by a stainless steel platen attached to the crosshead of the compression unit used to form the compacts. Again the crosshead descended at a rate of 1 mm min^{-1}. The load necessary to cause failure was determined by a calibrated load cell (Countant Tranducers) connected to a recording galvanometer (Metrohm Labograph).

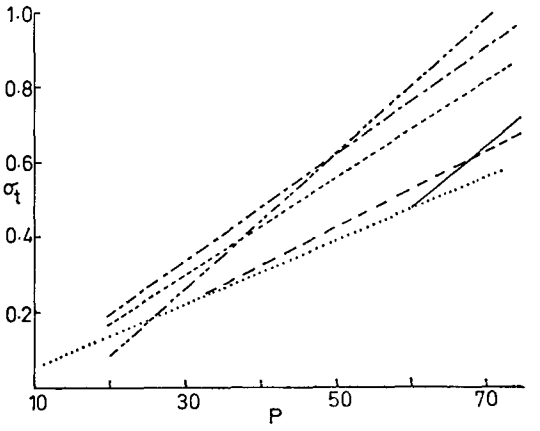

FIG. 1. Linear regression lines for the relation between applied pressure P (MNm^{-2}) and the tensile strength of tablets σ_t (MNm^{-2}) prepared from mixtures of phenacetin and dicalcium phosphate. % of dicalcium phosphate: ——— 0, — — — 20, — · — 40, — — — — 60, – – – – 80, · · · · 100.

A necessary requirement for the application of previous procedures for predicting the strength of mixed component tablets is to be able to produce tablets of each material individually. In the present work, the compaction of phenacetin presented difficulties, but by slow removal of the applied pressure and slow ejection from the die, tablets could be prepared over a limited pressure range. For all the blends and the individual materials there was a linear relation between the applied pressure P and the tensile strength of the compact σ_t derived from the diametral compression test; see Fig. 1. These relations allow the estimation of the tensile strength of tablets at any chosen pressure.

In the previous work, tablets of mixed components were prepared at a single pressure. At all applied pressures, the tensile strength of tablets of dicalcium phosphate and phenacetin are generally higher than those which would be predicted by consideration of the tensile strength of the individual materials. In addition because of the differing rates of change of tensile strength with applied pressure, the relation between tensile strength and tablet composition depends on the formation pressure (see Fig. 2). This situation does not appear to exist with mixtures of lactose. The possible sources of the difference between

* Correspondence.

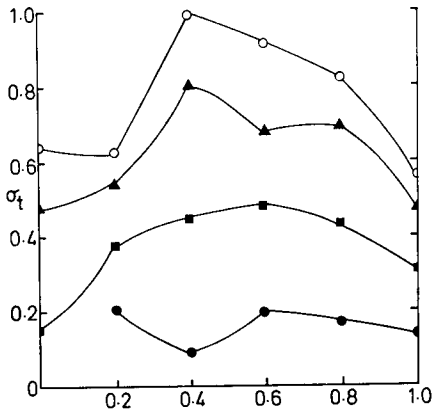

FIG. 2. Tensile strength of tablets (σ_t) prepared at ● 20, ■ 40, ▲ 60 and ○ 70 MN m^{-2} as a function of dicalcium phosphate-phenacetin composition. Ordinate—Fraction of dicalcium phosphate.

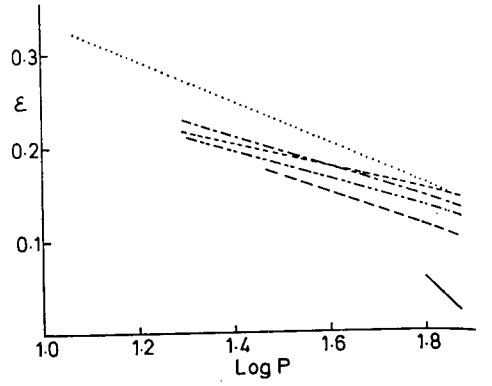

FIG. 3. Linear regression lines for the relation between log applied pressure (P) and the porosity (ϵ) of tablets prepared from mixtures of phenacetin and dicalcium phosphate. % of dicalcium phosphate; ——— 0, — — — 20, — — — 40, — — — — 60, — — — 80, · · · · · 100.

the present results and those for lactose systems are presumably linked to the structure of the tablet, which will influence particle contacts and the propagation of cracks during the strength test, and the types of bonding systems involved. Compaction can result in the formation of dicalcium phosphate-dicalcium phosphate: phenacetin-phenacetin and/or dicalcium phosphate-phenacetin bonds. The presence of a higher strength than predicted suggests that the bond between the differing materials is in fact stronger than that between the individual materials themselves. Before accepting such a conclusion it is essential not to neglect the tablet structure. The structural property which can readily be calculated from the tablet dimensions and particle density is the porosity of the tablet, ϵ. The relation between this property and the logarithm of the applied pressure was found to be linear, as shown in Fig. 3. From these relations the porosity of the tablet at the applied pressure used for comparison of tensile strengths can be obtained. The possible application of a correction factor for porosity $(1/(1-\epsilon)$ in the calculation of tensile strength was considered by Newton, Rowley & others (1971) and used by Rowe, Elworthy & Ganderton (1973). Incorporation of such a factor does not however alter the general shape of the relation between strength and composition shown in Fig. 2.

The other feature of Fig. 3 is the large difference in porosity between tablets containing phenacetin alone and tablets which contain dicalcium phosphate in any proportion. Thus it is not possible to compare the tensile strength of tablets of equal porosity (a linear relation in fact exists between porosity and the logarithm of the tablet tensile strength). This large difference in porosity suggests a possible cause of the failure to be able to predict the tensile strengths of mixed component tablets. When as previously (Fell & Newton, 1970b) different types of lactose are compared there is no major difference in the mechanisms involved in volume reduction. In the present study, the two materials obviously consolidate by different mechanisms. The phenacetin undergoes very large volume reductions on the application of quite low pressures. Representation of the results of changes in tablet relative density with applied pressure by the method suggested by Heckel (1961) clearly shows that phenacetin undergoes far greater particle rearrangement before bonding occurs than does dicalcium phosphate. Thus if materials consolidate by differing mechanisms, it appears that it will not be possible to predict the strength of tablets prepared from mixtures of such materials.

The mechanisms of increasing tablet strength by mixing ingredients could involve the prevention of crack propagation, as discussed for composite materials by Gordon (1973).

The ability to produce tablets of greater strength than the individual component materials provides the possibility of new concepts in designing tablet formulations.

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Crystal modification of methisazone by grinding

KOK CHYE LEE, J. A. HERSEY*, *Victorian College of Pharmacy, 381 Royal Parade, Parkville, Victoria 3052, Australia*

Methisazone (1-methylisatin 3-thiosemicarbazone) is an antiviral agent (Bauer, Dumbell & others, 1962). In the freshly prepared state it exists as long fibres, possessing low solubility, poor absorption, low bulk density and poor flow properties (Axon, 1972). It is used in various pharmaceutical formulations as freshly ground material, where there is a ten-fold increase in dissolution rate and accompanying increased bioavailability. The freshly ground material has a marked tendency to revert to the original fibrous crystals on storage; this crystal growth has been described as outgrowths of 'whiskers' (Deavin & Mitchell, 1965).

The above results suggest a crystal modification of methisazone occurs on grinding to form an unstable polymorph (or amorphous form). Florence, Salole & Stenlake (1974) have reported that similar modifications occur during the grinding of digoxin.

We have examined infrared spectra and carried out X-ray diffraction and differential thermal analysis on three samples of methisazone—unground and micronized material as obtained from Burroughs Wellcome and freshly ground material, formed by ball—milling some of the unground material from the same source.

X-ray diffraction patterns were obtained using a Toshiba Model ADG–301 diffractometer with nickel filtered copper radiation at a scan speed of 0·5° min^{-1}. All three materials gave distinctive diffraction patterns (Fig. 1), indicating the presence of different polymorphic forms (Pfeiffer, Yang & Tucker, 1970). Recrystallized material formed by either slow recrystallization from dimethyl sulphoxide or by seeding with unground material gave a different defraction pattern from material formed by adding water to the solution in dimethylsulphoxide.

In the differential thermal analysis study, slight differences in the endothermic peak commencing about 239° were observed for the materials using a Mettler TA2000 (Fig. 2). The presence of a shoulder on these peaks indicates a phase change before melting, observed microscopically using a hot-stage. With different polymorphic forms of oxyclozanide, Pearson & Varney (1973) also found only slight differences in thermal properties.

Similar slight differences were obtained in infrared spectra using Nujol mulls in a Perkin Elmer, Model 337

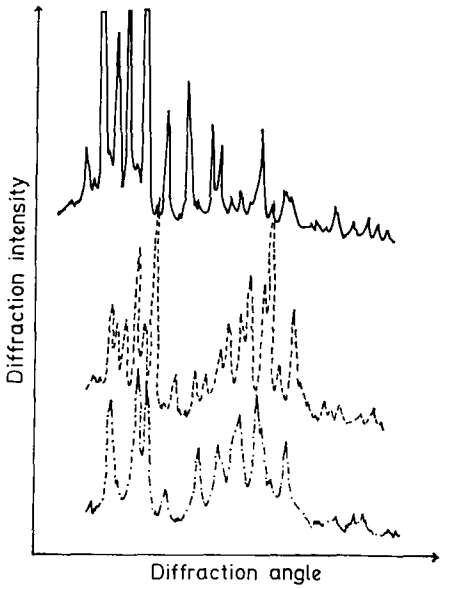

FIG. 1. X-Ray diffraction patterns of: unground methisazone ———, micronized methisazone – – –, milled/ground methisazone .–.–.

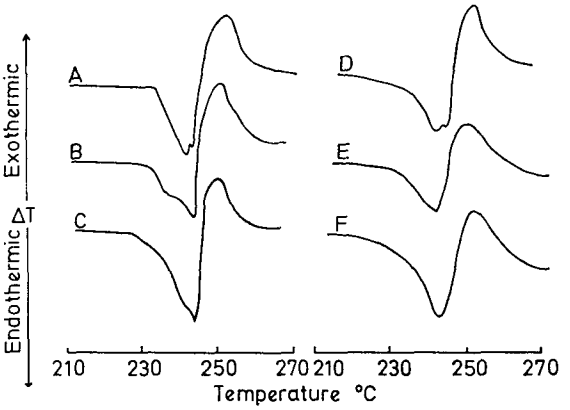

FIG. 2. D.T.A. traces of: A unground methisazone, B micronized methisazone, C milled/ground methisazone, D methisazone precipitated by water, E methisazone obtained by seeding, F methisazone obtained by slow recrystallization.

* Correspodence