(iii) (above). CPZ and CPZSO and their demethylated analogues were clearly identified (by reference to standards) in the extract of the non-reduced sample. The extract from the reduced sample showed increased signals for CPZ and CPZSO, indicating that CPZNO and CPZNOSO were originally present. Additionally, there was an increase in the demonomethylchlorpromazine signal, and this was found to result from partial conversion of CPZNO to this compound when treated with $Na_2S_2O_5$, by g.l.c. and by thin-layer chromatography on silica gel using the standard method. This conversion, which yields formaldehyde, appears not to have been previously reported. It has obvious implications for CPZNO assays. In this case, standards and tests were assayed in parallel and a similar degree of conversion occurred in each case.

As implicit in Fig. 1, CPZNO and CPZNOSO were both found in urine. Concentrations of these compounds in all three patient groups ranged from 0·07 to 0·11 μg ml^{-1}, which was about the range of unmetabolized CPZ and CPZSO in the same urine samples. Concentrations of CPZNO in plasma were lower while no CPZNOSO was detected. Patients in group (iii) showed no CPZNO, no increase in the CPZ signals being detected even when a 10 ml pooled plasma sample was studied. In the other groups, CPZNO concentrations were 5·6–7·3 ng ml^{-1}, one third to one half of the CPZ concentrations 11·3–23·2 in the same patients. Thus CPZNO is sometimes present in plasma during treatment, although it appears to be cleared quite rapidly.

CPZNO is also extractable from plasma into ether, from which it is back extractable into 0·1N HCl. When present, it will therefore appear as CPZ and as desmonomethylchlorpromazine in g.l.c. traces of ether extracts of plasma designed specifically to detect CPZ.

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The compression properties of magnesium and calcium carbonates

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Tablets are traditionally made by either wet or dry granulation, but both methods are expensive in time, labour, space, equipment and power. Direct compression, which consists only of mixing and compaction stages, offers economies in all these areas, but depends for success upon certain properties of the final mixture. The technique, extensively reviewed by Livingstone (1970), Kanig (1970) and Khan & Rhodes (1973a), has, however, the disadvantage of requiring commercially available materials which are expensive compared with the more traditional tablet fillers. For this reason the compressional properties of several substances, traditionally found in development laboratories, were studied. This paper discusses the tableting properties of magnesium and calcium carbonates.

Materials: heavy magnesium carbonate, B.P. (Newalls Insulation Ltd, Washington, Co. Durham), magnesite, naturally occurring anhydrous magnesium carbonate, (Hopkins and Williams, Chadwell Heath, Essex) and heavy calcium carbonate (J. and E. Sturge Ltd, Birmingham). The heavy magnesium carbonate had a mean particle size of 55 μm. The magnesite was finer, 75% being less than 32 μm. The calcium carbonate —the coarsest grade available, had a mean particle size of 35 μm. These materials were blended with 5% sodium starch glycollate and 0·5% magnesium stearate and compressed on an instrumented single punch tableting machine (F3, Manesty Machines Ltd, Speke) fitted with 3/8 inch flat-faced punches. The instrumentation consisted of a four arm, semi-conductor strain gauge bridge (Kulite Semiconductor Ltd, Basingstoke) bonded onto the upper eccentric arm of the tableting machine. A constant direct current was applied from a bridge supply and balance unit (Fylde Electronic Laboratories Ltd, Preston), and the signal from the bridge was recorded using a storage oscilloscope (5103N series, Tektronix U.K. Ltd, Harpenden).

Tablet crushing strength was measured using an Erweka tester (Erweka-Apparatebau G.m.b.H., Offenbach, West Germany). Friability was measured by rotating the tablets 1000 times in a stainless steel

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cylinder 7·5 cm long, at 1 rev s^{-1}. Disintegration time was assessed using the standard British Pharmacopoeia apparatus.

Some tableting properties of the compositions of heavy magnesium and calcium carbonates are shown in Figs 1 and 2. No results can be presented for magnesite as it did not flow well enough to fill the tablet die. The addition of 0·5% Aerosil to the formulation greatly improved the flow, but satisfactory tablets could not be formed. They were extremely friable and very soft even when compressed at 2000 kg cm^{-2}. Capping also occurred at this and lower pressures. The differences between the tableting properties of this material and heavy magnesium carbonate are very marked. The latter did not cap over the pressure range studied but produced very strong tablets displaying flash dispersibility. In fact, even at 5000 kg cm^{-2}, when the compacts were too strong to break using the Erweka tester, they disintegrated in less than 30 s. The heavy calcium carbonate showed intermediate properties. The composition flowed well and compacts could be formed al-

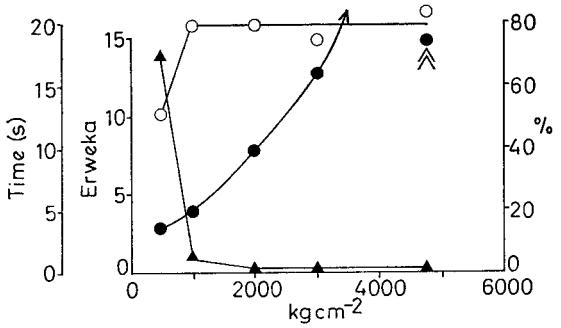

FIG. 1. Heavy magnesium carbonate. Axes—x axis—compression pressure (kg cm^{-2}.) y axes—1st axis—disintegration time (s), 2nd axis—crushing strength (Erweka), 3rd axis—friability (%). ○ Disintegration time. ● Crushing strength. ▲ Friability.

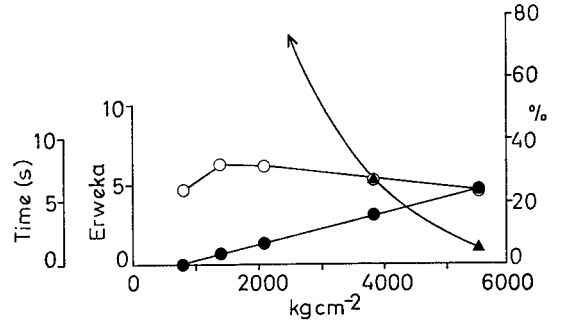

FIG. 2. Heavy calcium carbonate. Axes—x axis—compression pressure (kg cm^{-2}). y axes—1st axis—disintegration time (s), 2nd axis—crushing strength (Erweka), 3rd axis—Friability (%). ○ Disintegration time. ● Crushing strength. ▲ Friability.

though they were fairly weak. Their maximum crushing strength at 5000 kg cm^{-2} was only 5 units using the Erweka tester and their friability at this pressure was ten times as great as the heavy magnesium carbonate compacts. However, there were no signs of capping over the pressure range studied and the compacts disintegrated very rapidly in water.

The differences in the compaction properties of heavy magnesium carbonate and the other carbonates described above might well be due to the water of crystallization present in the heavy magnesium carbonate. Martindale (1958) gives its formula as $3MgCO_3$, $Mg(OH)_2$ $4H_2O$. Jaffe & Fosse (1959) showed that substances with water of crystallization which formed good tablets could not be tableted when this water was removed, considering that the water of crystallization acted as a 'built-in' binding agent. Similarly Gregory (1960) suggested that a high moisture content favoured the plastic deformation of an otherwise brittle substance, thus aiding compression.

It is unlikely that the differences in particle size of the magnesium and calcium carbonates are significantly contributing to differences in compaction behaviour. I have previously shown (1971) that when the mean particle size of heavy magnesium carbonate is reduced from 61·5 to 39·5 μm, the density of the compacts formed by compression on a hydraulic press increases.

The chemically basic nature of heavy magnesium carbonate might be considered a disadvantage when using it as a directly compressible excipient. It is often claimed that pharmaceutical excipients should be physically, chemically and pharmacologically inert; however, the high pKa of magnesium carbonate may make it an ideal adjuvant when used with a drug of low pKa. Many drugs in common use fall into this category, e.g. aspirin, the barbiturates, many penicillins and cephalosporins. Accordingly, tablets containing 250 mg of benzylpenicillin were made by direct compression using either heavy magnesium carbonate B.P. or unmilled dicalcium phosphate dihydrate as excipient. Unmilled dicalcium phosphate dihydrate is a well-established direct compression excipient and has been described recently by Khan & Rhodes (1973b). The composition consisted of benzylpenicillin 45%, excipient 45%, sodium starch glycollate 7%, sodium lauryl sulphate 2%, magnesium stearate 1%. The powders were compressed at 1300 kg cm^{-2}. The tablets containing magnesium carbonate had a mean crushing strength of 8 on the Erweka scale whereas those containing dicalcium phosphate had a crushing stength of 5·5. The dissolution rates of the tablets, measured at pH 1·5 using a round bottom flask and stirrer method (stirring rate 60 rev min^{-1}), are shown in Fig. 3. The benzylpenicillin was released much more rapidly from the tablets containing magnesium carbonate than from those containing dicalcium phosphate, the respective times for 50% dissolution being 6 and 16 min. An important property of a directly compressible excipient is

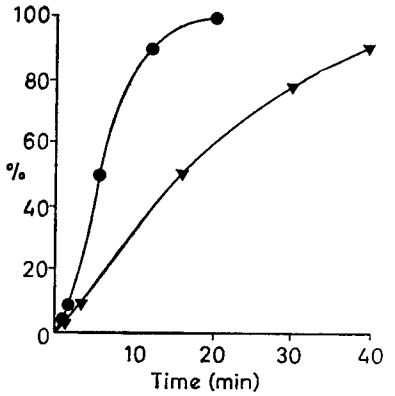

FIG. 3. Dissolution of benzylpenicillin tablets. y axis—% dissolved. ● Magnesium carbonate formulation. ▼ Dicalcium phosphate formulation.

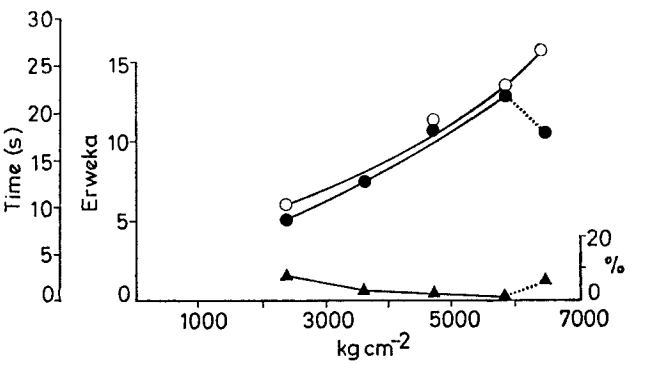

FIG. 4. Heavy magnesium and calcium carbonate (1:1 mixture). Axes—x axis—compression pressure (kg cm^{-2}). y axes—1st axis—disintegration time (s), 2nd axis—crushing strength (Erweka), 3rd axis—friability (%). ○ Disintegration time. ● Crushing strength. ▲ Friability.

its capacity, i.e. its ability to be used with a large percentage of a poorly compressible active material without undue loss of overall compressibility. The benzylpenicillin tablets quoted above illustrate that as good, if not better, quality tablets can be made using heavy magnesium carbonate as by using unmilled dicalcium phosphate, a well-established direct compression excipient. The capacity of heavy magnesium carbonate can also be illustrated by replacing half of it in the original composition with heavy calcium carbonate. Some tableting properties of this mixture are shown in Fig. 4. It can be seen that although at, say, 3000 kg cm^{-2}, the crushing strength of the mixture is half that of magnesium carbonate, it is almost three times that of calcium carbonate. Similarly at 4000 kg cm^{-2} although the mixture is some three times as friable as heavy magnesium carbonate, it is ten times less friable than calcium carbonate.

To ensure uniformity of tablet weight, direct compression excipients should possess good flow properties. Tablets of heavy magnesium carbonate were therefore compressed on a rotary tableting press (D3 Manesty Machines Ltd, Speke) using 5/16 inch, normal concave punches. Three hundred tablets were taken at random from the middle of the run, weighed, and the coefficient of weight variation calculated. A similar test was carried out with Celutab (now Emdex, Kingsley and Keith Chemicals Ltd, Croydon) and Nutab (Mallinckrodt (U.K.) Ltd, Ashford), two materials sold specifically as direct compression excipients. These were first mixed with 1% magnesium carbonate. The coefficients of variation were 1·41, 1·64 and 1·68% respectively.

Of the three alkaline earth carbonates studied, heavy magnesium carbonate B.P. showed by far the best compaction properties. It can be compressed to give tablets with high crushing strength, low friability and yet almost immediate disintegration. Compacts prepared on a rotary tableting machine showed a weight variability comparable with that of materials sold specifically as direct compression excipients. Tablets containing active materials of low pKa and heavy magnesium carbonate gave enhanced dissolution rates at gastric pH.

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