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Effects of applied load and particle size on the plastoelasticity and tablet strength of some directly compressible powders

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Correlations have been established between the particle size and packing fraction of microcrystalline cellulose, calcium phosphate dihydrate, corn starch and lactose, and the elastic recovery, stress relaxation, and tensile strengths of their tablets.

Numerous studies have been made of the elastic and plastic deformation of pharmaceutical powders during their compression into tablets. (Seitz & Flessland 1965; Cole et al 1975; David & Augsburger 1977; Hiestand et al 1977; Malamataris et al 1984; Bangudu & Pilpel 1985; Esezobo & Pilpel 1986; Ejiofor et al 1986.) This communication gives further experimental data on the effects of particle size and of packing fraction (achieved by applying different compression loads) on the elastic recovery ER, stress relaxation SR, the ratio ER/SR and on the tensile strengths of tablets made from four directly compressible pharmaceutical excipients.

Materials and methods

The materials were microcrystalline cellulose (Avicel PH 101, Honeywell and Stein); calcium phosphate dihydrate (Emcompress, Albright and Wilson); corn starch (Sta-Rx 1500, Colorcon) and lactose (spray dried, McKesson and Robbins).

Each material, except Avicel which was only available in the size <63 μm, was sieved into fractions between <63 and 355 μm diameter, dried to less than 2% w/w moisture by heating and storing in a vacuum and the particle densities were determined with a Model 930 air comparison pycnometer.

Three replicate 450 mg samples of each material were formed into 10 mm diameter, flat faced tablets in a Dartec M 2501 universal tester and values of ER and SR were measured from the changes in dimensions of the tablets during application and release of pressure as previously described (Malamataris et al 1984; Bangudu & Pilpel 1985; Ejiofor et al 1986). The thicknesses of the tablets varied between about 4·0 and 4·5 mm due to the different true densities of the materials but this had a relatively small effect on ER/SR (Bangudu & Pilpel 1985). The tensile strengths of the tablets were obtained by diametral compression using a CT 40 tester (Fell & Newton 1970). Replicate values generally agreed to within ± 10% of each other.

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Results and discussion

For any particular particle size, an increase in the compression load caused an increase in packing fraction and in all cases resulted in an increase in ER, a decrease in SR (except for lactose which is known to be brittle) and, in general, an increase in ER/SR (Fig. 1) the effects being greatest with Avicel and Sta-Rx.

The higher values of ER/SR for Avicel and Sta-Rx than for Emcompress and lactose at high applied loads (>20 kN) and at high packing fractions (>0·9) are due to the essentially different plastoelastic properties of the

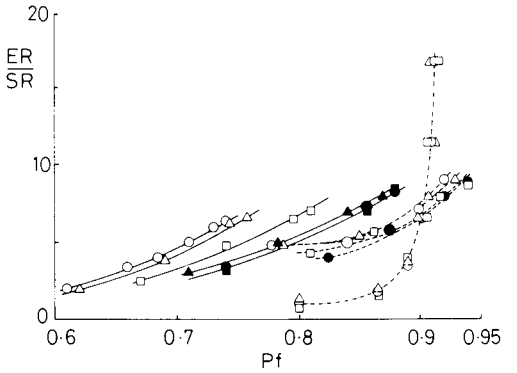

FIG. 1. Effect of particle size and packing fraction on ER/SR for Emcompress, Lactose and Sta-Rx. —— Emcompress. - - - - Lactose. -·-·-·- Sta-Rx. Mean particle size (μm): ○——○ 31·5, △——△ 76·5, □——□ 120·0, ▲——▲ 165·0, ●——● 215·0, ■——■ 302.5.

two classes of materials (Cole et al 1975; Rees & Rue 1978; Krycer et al 1982). At a fixed packing fraction of 0·74 for Emcompress, 0·81 for Avicel, 0·85 for Sta-Rx and lactose, ER/SR decreased with increase in particle size, the effect being in the order Emcompress ≫ lactose > Sta-Rx (see Fig. 1).

The tensile strengths of the tablets varied with packing fraction and with particle size. At the above values of packing fraction, there was a correlation between tensile strength and particle size as shown in Fig. 2. (See also Adeyemi & Pilpel 1984; Ragnarsson & Sjogren 1985.) Also for Emcompress and lactose there was a correlation between ER/SR and particle size, but

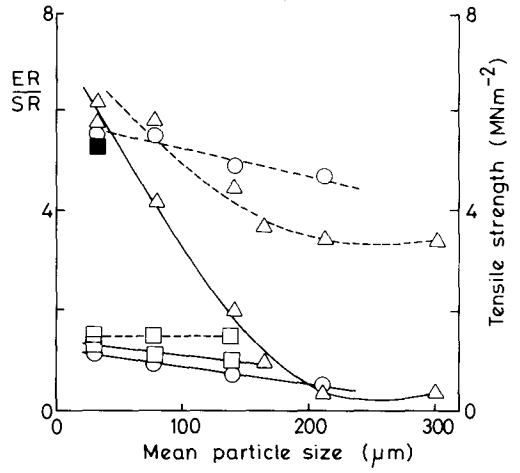

FIG. 2. Effect of particle size on ER/SR and tensile strength for Emcompress at $\rho_f = 0{\cdot}74$, lactose at $\rho_f = 0{\cdot}85$ and on the tensile strength of Sta-Rx at $\rho_f = 0{\cdot}85$ and Avicel at $\rho_f = 0{\cdot}81$. - - - - ER/SR, —— Tensile strength, △——△ Emcompress, ○——○ Lactose, □——□ Sta-Rx, ■ Avicel.

not for Sta-Rx whose value remained approximately constant at 1·5 (Fig. 2). No explanation can be offered for the greater effect of particle size on ER/SR for Emcompress than for the other materials.

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Central muscarinic activation elicits compulsive drinking behaviour in the rat

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Injection of bethanechol into the lateral cerebral ventricle of the rat induces a marked increase in drinking, within 30 min from administration. The response is dose-related, maximal water intake (6·1 ± 0·55 mL; mean ± s.e.) occurring at 10 μg of bethanechol. Peripheral administration of the agonist (up to 3 mg kg^{-1} i.p.) fails to elicit drinking. Among several specific antagonists only anti-muscarinic drugs produced a significant inhibition of the response, suggesting that the compulsive drinking behaviour in the rat is caused by activation of central muscarinic receptors. The drinking behaviour emerges as a reliable test to assess central muscarinic activity of both agonists and antagonists.

Central cholinergic stimulation by carbachol induces a short latency drinking response in the rat (Grossman 1960; Swanson & Sharpe 1973; Hoffman & Phillips 1977; Menani et al 1984). A similar effect is also exhibited by angiotensin II (Epstein et al 1970; Swanson & Sharpe 1973; Hoffman & Phillips 1977), acting, however, through an independent peptidergic pathway, as demonstrated by its sensitivity to the specific antagonist, saralasin (Giardina & Fisher 1971; Hoffman & Phillips 1977). Whether central muscarinic receptors activated by carbachol are solely responsible for the dipsogenic response remains uncertain, since hexamethonium, applied to the subfornical area, produces a partial blockade (Menani et al 1984). Moreover, nicotine, when applied centrally, causes a moderate but measurable increase of water intake (Stein & Seifter 1962). To avoid possible direct nicotinic stimulation we have studied the drinking behaviour induced by intraventricularly (i.vt.) applied bethanechol, a muscarinic agonist devoid of the nicotinic stimulating properties of carbachol, yet resistant to hydrolysis by cholinesterases (Taylor 1985). In addition we have tested specific antagonists of different receptor systems for their effect on bethanechol-induced water intake.

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