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Continuous matrix formation for controlled drug release: compression of isotropic polymeric system

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The compaction of a powdered solid within the confines of a die between two punches is complex, and numerous simultaneous internal processes lead to consolidation and bonding. These events include particle rearrangement, fracture and plastic deformation (Hiestand et al., 1977; Carstensen, 1973; Fell and Newton, 1971). With materials of low melting point, localized melting at the asperities of contact points occurs (Rankell and Higuchi, 1968; York and Pilpel, 1973). Compression behaviour of powders is conveniently characterized by Heckel plots (Heckel, 1961) and various authors have successfully applied Heckel's equation to pharmaceutical powders to identify the types of mechanism occurring during compression (Hou and Carstensen, 1985; Roberts and Rowe, 1985; Hersey and Rees, 1971; York and Pilpel, 1973).

Considerable efforts in research are under way to adapt polymeric systems for drug delivery and release. The purpose of the present work is to report the compression behaviour of polymers and their mixtures with active drug material in relation to tabletting.

The materials examined in this study were chosen because they are among the more commonly used polymers in matrix release formulation. They were used as received from the respective manufacturers: PEG 6000 (BDH-Chemical, Poole, U.K.), Eudragit SR (Rohm Pharma, Darmstadt), ethylcellulose (Hercules Powder Co.), and theophylline crystals, commercial grade, lot 1028.

The proportion of each material used is shown in Table 1. A solid dispersion technique described previously (Fassihi et al., 1985) was used and selected fractions of powders were directly compressed into tablets of 400 mg using 10 mm flat

TABLE 1

COMPOSITION OF POLYMERIC MIXTURES USED FOR COMPRESSION [a]

Formulae	I [b]	II [b]
PEG 6000	40	30
Eudragit SR	30	20
Ethyl cellulose	20	20
Stearyl alcohol	10	10
Theophylline	–	20

[a] Quantities listed are percentage by weight.

[b] The true densities for mixture I and II is 1.45 ($g \cdot cm^{-3}$) and 1.62 ($g \cdot cm^{-3}$), respectively.

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punches. Compression was carried out using an instrumented Manesty F3 single punch machine at a constant punch velocity, with pressure ranging from 100 to 1150 $kg \cdot cm^{-2}$. To attain a more homogeneous compact in regard to pressure–density distribution a Manesty B3 rotary machine fitted with 7.5 mm standard concave punches was used. One batch of formulation (I) was tabletted on a rotary machine at applied pressure immediately below the critical zone (see text). True densities of the polymeric mixtures were determined by pouring a molten mixture into an aluminium mold of known volume. After solidification the mass was removed and the true density ρ_t calculated.

The powder mixtures obtained by solid dispersion technique will give rise to an isotropic homogeneous system, which in turn upon compression will result in a compact of low stress gradient with defined regions of different relative density. The presence of stearyl alcohol and polyethylene glycol will reduce both interparticle friction and friction between the surfaces of the punch and die. The Heckel equation (Heckel, 1961) was used to analyse the relationship between the relative density measured during compaction and the applied pressure. By plotting graphs of $\ln(1/(1-D))$ versus compression force, it should be possible to test the applicability of the Heckel equation to isotropic polymeric systems (Fig. 1). Results illustrate that the relationship between the deformation resistance of a polymeric system and the product of the compression force and relative density is not linear. The curves are initially steep and linear at the low-pressure end of the graph (up to 400 $kg \cdot cm^{-2}$) and become gradually flatter with a distinct negative deviation as compression force and relative density increase. The pattern of deformation of the polymeric systems under stress may thus be related to the component which is predominantly plastic in its response at the lower pressure range. The presence of theophylline in formulation (II) tends to oppose a plastic deformation mechanism and significantly reduces the compressibility of polymeric mixtures.

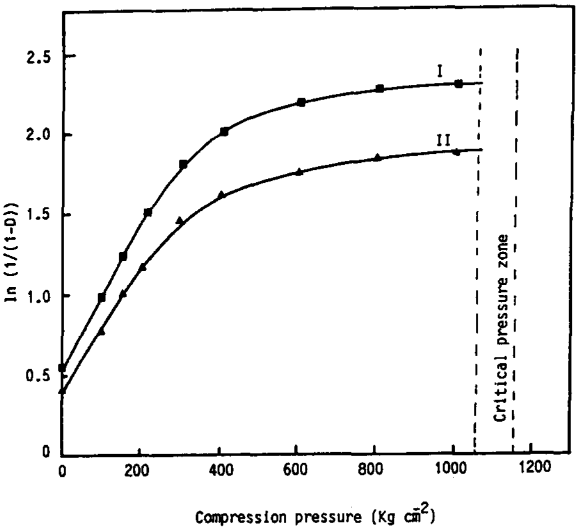

Fig. 1. Heckel plots of polymeric mixture 'I' and drug–polymer mixture 'II' using flat-faced punches.

The sharp break in the curve probably corresponds to the pressure at which all the void spaces between the particles are filled and the polymer particles begin to fuse. As density of the material under pressure approaches the true density of the powder, then $\ln(1/(1-D))$ approaches infinity and rapid curvature of the plots occurs. An interesting feature is complete melting of the compact at a critical applied pressure (above 1000 $kg \cdot cm^{-2}$), suggesting considerable squashing of contact points and probably a drop in the melting temperature, the latter phenomenon having previously been documented (Rankell and Higuchi, 1968; York and Pilpel, 1972, 1973).

Train (1956) investigated the distribution of pressures and densities within a compact and his findings suggest that the regions of high density and pressure correlate well (i.e. at the edge of the upper punch, where the pressure is applied). Compression involving movement of both upper and lower punches should therefore significantly reduce the density variation within a compact. Several factors, however, may influence the structure of a compact and the magnitude of pressure distribution at the maximum compression force. When isotropic homogeneous powders were compressed on a rotary machine, regions of greatest density were produced in a peripheral ring parallel with and near to the points of greatest pressure. Scanning electron micrographs of fractured edges and bulk of tablets were taken (see Figs. 2 and 3),

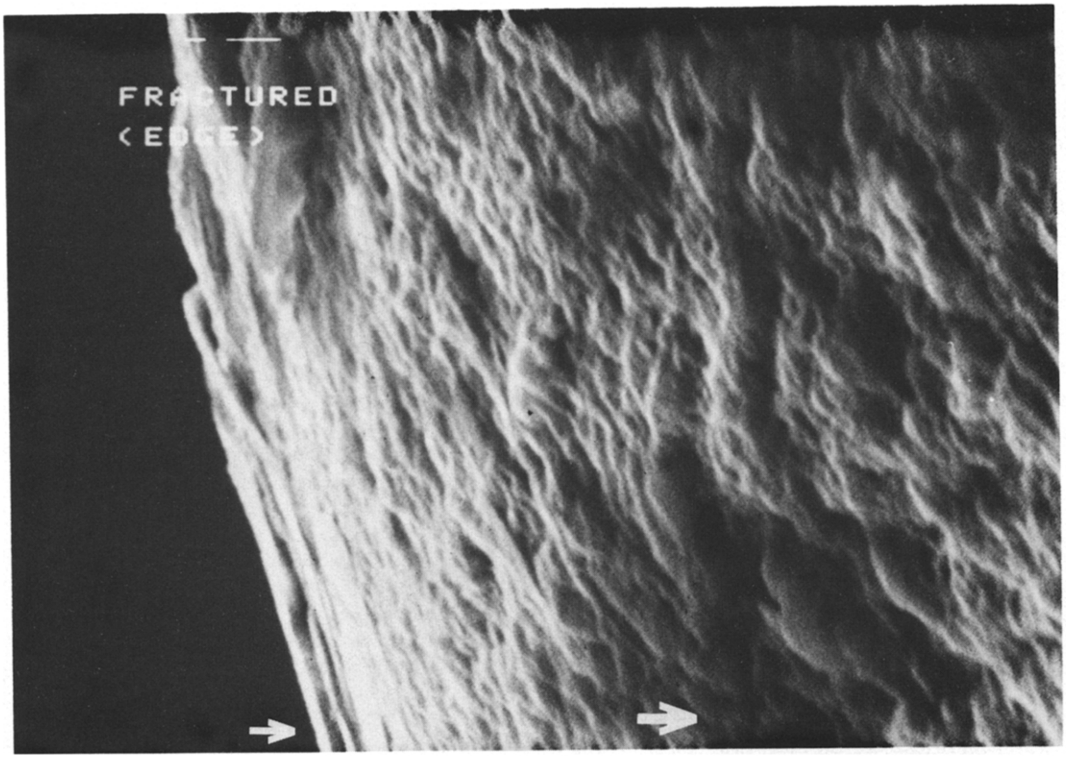

Fig. 2. SEM photomicrograph of fractured (edge) tablet showing a decrease in density towards the bulk of the tablet.

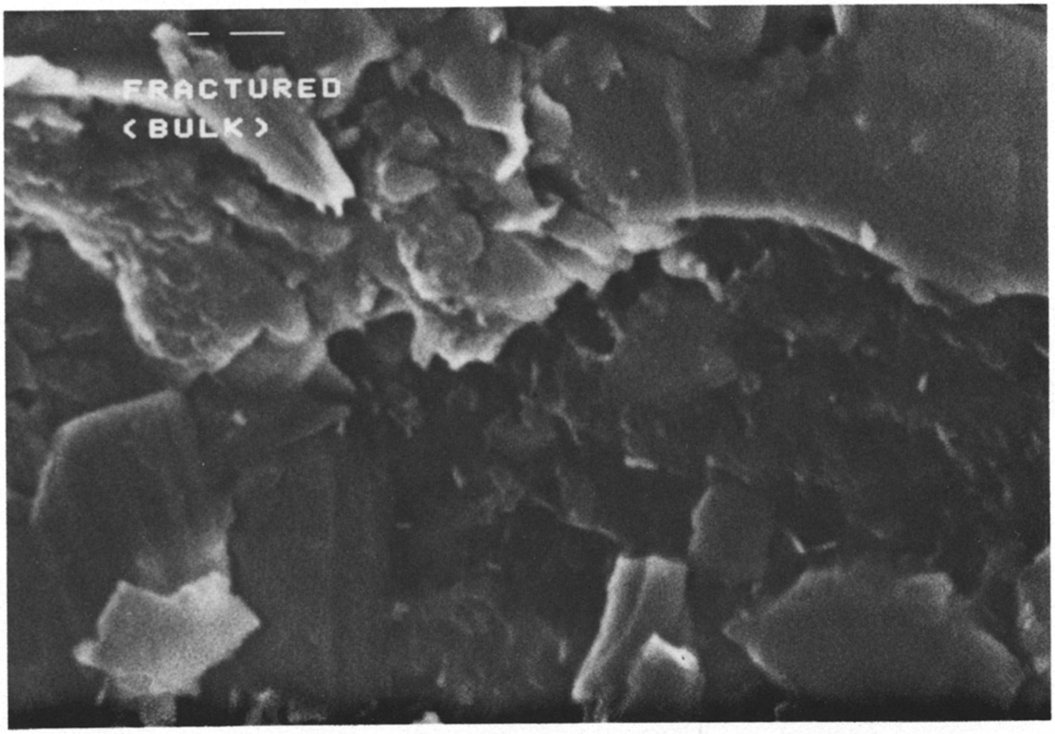

Fig. 3. SEM photomicrograph of fractured bulk, showing the extent of porosity.

and served to demonstrate the existence of high density areas adjacent to the surfaces. Fig. 3 shows the bulk structure of the fractured compact at the same magnification as Fig. 2, clearly indicating the lower degree of consolidation in the central part of the tablet. Thus mechanical energy is converted to thermal energy (Bowden and Ridler, 1936; Fassihi et al., 1977), causing surface melting. As the pressure applied by the upper and lower punches is exerted only on particles directly in contact with the punch surfaces, very high pressure develops at small individual points of contact, thus forming localized hot spots. Such high temperature areas can attain the melting point of the substance being compressed.

In conclusion it may be noted that two trends are apparent from the Heckel plots. Firstly, the curves are initially steep indicating the compressibility of the polymers. Secondly, as compression force increases, the slope decreases indicating a decrease in the rate of densification. It is shown that, in the case of the formulations studied, a polymeric mixture obeys the Heckel relationship only at low pressures (not exceeding 400 $kg \cdot cm^{-2}$). At higher pressures plastic deformation predominates and asperity melting occurs. When the pressure reaches the critical zone, particles in direct contact with punch surfaces melt and produce a continuous film. A further increase in pressure beyond the critical zone may result in complete melting.

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References

Bowden, F.P. and Ridler, K.E.W., Measurement of surface temperatures thermo-couple method. *Proc. R. Soc. London, Ser. A*, 151 (1936) 610–623.

Carstensen, J.T., *Theory of Pharmaceutical systems, Vol II*, Academic Press, New York, 1973, p. 209.

Fell, J.T. and Newton, J.M., Assessment of compression characteristics of powders. *J. Pharm. Sci.*, 60 (1971) 1428–1429.

Fassihi, A.R., Davies, P.J. and Parker, M.S., Effect of punch pressure on the survival of fungal spores during the preparation of tablets from contaminated raw materials. *Zbl. Pharm.*, 116 (1977) Heft 12, 1267–1271.

Fassihi, A.R., Parker, M.S. and Poorkavoos, N., Solid dispersion controlled release: effect of particle size, compression force and temperature. *Drug. Dev. Ind. Pharm.*, 11 (1985) 523–535.

Hiestand, E.N., Wells, J.E., Peot, C.B. and Ochs, J.F., Physical processes of tableting. *J. Pharm. Sci.*, 66 (1977) 510–519.

Heckel, R.W., Density-pressure relationships in powder compaction. *Trans. Metal. Soc. A.I.M.E.*, 221 (1961) 671–675.

Hou, X.P. and Carstensen, J.T., Compression characteristics of basic tricalcium phosphate. *Int. J. Pharm.*, 25 (1985) 207–215.

Hersey, J. and Rees, J., Deformation of particles during briquetting. *Nature (London)*, 230 PS (1971) 96.

Roberts, R.J. and Rowe, R.C., The effect of punch velocity on the compaction of a variety of materials. *J. Pharm. Pharmacol.*, 37 (1985) 377–384.

Rankell, A.S. and Higuchi, T., Physics of tablet compression. XV. *J. Pharm. Sci.*, 57 (1968) 574–577.

Train, D., An investigation into the compaction of powders. *J. Pharm. Pharmacol.*, 8 (1956) 745–761.

York, P. and Pilpel, N., The effect of temperature on the mechanical properties of some pharmaceutical powders in relation to tableting. *J. Pharm. Pharmacol.*, 24 (1972) 47P–56P.

York, P. and Pilpel, N., The tensile strength and compression behaviour of lactose, four fatty acids and their mixtures in relation to tableting. *J. Pharm. Pharmacol.*, 25 (1973) 1P–11P.