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COMMUNICATIONS

A consideration of experimental variables in the analysis of powder compaction behaviour

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Numerous equations have been proposed to describe the compaction process taking place when powders are compressed in dies, including those attributed to Walker (1923), Cooper & Eaton (1962) and Heckel (1961). However it is well recognized that no single equation adequately describes the various mechanisms involved (Bocksteigel 1972; Cole et al 1975). Recently, Rue & Rees (1978) have stated that caution should be observed when classifying powder compaction behaviour with respect to particle size on the basis of the Heckel equation since the type of plot obtained will vary depending on the experimental technique employed. They suggest an alternative technique which quantifies the degree of consolidation occurring by plastic deformation by measuring areas under Heckel plots for different contact times. (Contact time is defined as the duration of time when the upper punch is in contact with the die contents, Jones 1977).

Published results for the compaction behaviour of different size fractions of crystalline lactose, a powder examined according to the Heckel equation by several investigators under varying experimental conditions, are shown in Table 1. Values of ρ_{f_A}, packing fraction due to die filling and particle slippage and rearrangement, and mean yield pressure (m.y.p.), the latter being estimated from the reciprocal of the slope of the linear section of the Heckel plot, are given together with values of coefficient of variation wherever possible. Data from studies A to E indicate similar behaviour in that after separate curved sections at low pressures the plots become linear and coincident for the different size fractions examined. Such behaviour is explained by particle fragmentation and rearrangement at low pressures which eliminates particle size effects at high pressures (Hersey & Rees 1970). The numerical values of ρ_{f_A} and m.y.p. obtained in the various studies are dependent upon experimental conditions. For example, the degree and type of lubrication of the punches and die and the mode of filling the die would influence ρ_{f_A}, whilst measurement of compact dimensions under pressure will include a minor elastic deformation element which tends to give a lower value of m.y.p. compared with at pressure estimates (Fell & Newton, 1971). The latter effect is clearly demonstrated in Table 1. The elastic element can be observed and estimated using techniques developed by De Blaey & Polderman (1970, 1972).

Table 1. Published values of ρ_{f_A}, densification due to die filling and particle slippage and re-arrangement, and mean yield pressure (m.y.p.) for crystalline lactose.

Study	A	B	C	D	E	F
Compaction conditions	fast compaction released	slow compaction at pressure	slow compaction released	fast compaction at pressure	slow compaction at pressure	slow compaction at pressure
Density determination						
Number of size fractions examined	4	3	3	3	4	4
Die diameter (mm)	12·0	12·7	12·7	12·7	19·0	33·0
Lubricated state	unlubricated	lubricated	lubricated	lubricated	lubricated	unlubricated
ρ_{f_A}	—	0·751	0·753	0·738	0·692	—
(coefficient of variation)	—	(2·1%)	(2·4%)	(3·5%)	(3·9%)	—
m.y.p.—(MN m^{-2})	174·2	158·0	218·0	206·0	169·8	range 84·7–175·4
(coefficient of variation)	—	(8·7%)	(2·0%)	(11·1%)	(7·6%)	

Study A: Hersey & Rees (1970).
Study B, C, D: Fell & Newton (1971).
Study E: York (1978).
Study F: Hersey et al (1972).

Study F, using a slow compaction technique and at pressure compact dimension determination, reported non-coincident, divergent Heckel plots for crystalline lactose with the value of m.y.p. increasing as the particle size of the fraction decreased. However, a much larger punch and die size, 33 mm, was used compared with the other studies and may account in part for the modified type of behaviour.

In an attempt to examine the effect of some experimental variables, in particular punch and die size on powder compaction behaviour, two grades of microfine cellulose (Elcema P050 and Elcema P100) were examined using a metered hydraulic press. The former grade had a declared size range of 1–50 μm and the latter 1–100 μm. Both powders were compressed individually in each of two flat faced stainless steel punch and die units measuring 10 mm and 45 mm diameter respectively. Compact dimensions were determined at pressure for the two powders in both dies, and after release and complete elastic and strain recovery for compacts prepared using the 10 mm punch and die unit for both powders.

A summary of the results is shown in the Heckel plots in Fig. 1. For all plots continuously decreasing slopes without linear sections were observed up to the applied pressures used, which is in accord with a previous report for a granular grade of microfine cellulose (Rue & Rees 1978). It is thus not possible to calculate values of ρf_A and m.y.p. For compacts prepared in the smaller die and dimensions estimated at pressure, a distinct particle size effect is indicated in Fig. 1A with a separation of the two plots, the larger sized powder producing a denser compact for a given applied pressure. This effect is significantly reduced when the larger die is used, see Fig. 1B, with the two curves almost superimposed. Modified packing arrangement, reduced wall effect, modified distribution of forces within the powder bed during compaction may all contribute to the different behaviour observed. A corresponding change in compaction behaviour involving a reduction of particle size effect when samples were compressed in larger dies has been reported for sodium chloride fractions (Hersey et al 1972). Both microfine cellulose and sodium chloride are thought to consolidate by plastic deformation (Rue & Rees 1978; Hardman & Lilley 1970).

When the dimensions of compacts prepared in the smaller die were determined after die release, the Heckel plots for the two powders, see Fig. 1C, are inverted compared with at pressure results, with the smaller size powder now giving denser compacts for a given applied pressure. This reversal of behaviour can be explained by compacts prepared from the 1–100 μm sized cellulose powder undergoing a greater degree of elastic and strain recovery compared with compacts prepared from the smaller size powder. Similar behaviour is likely to occur with other materials which exhibit a high degree of elastic and strain recovery after pressure removal and release from the die such as methyl-cellulose powders (York & Baily 1977).

In order to quantify compaction parameters for powders it would appear necessary to take into account a large number of experimental conditions. Not only variables such as history of powder, mode of die filling, rate of compaction, contact time and the state and type of lubrication should be recognized, but also the dimensions of the die and the technique used to estimate compact dimensions, the latter in particular for materials exhibiting a marked degree of elastic deformation. When analysing powder compaction data according to the Heckel equation, quantitative assessment of certain parameters such as ρf_A, m.y.p. or degree of plastic deformation for stated experimental conditions is possible enabling comparisons to be made

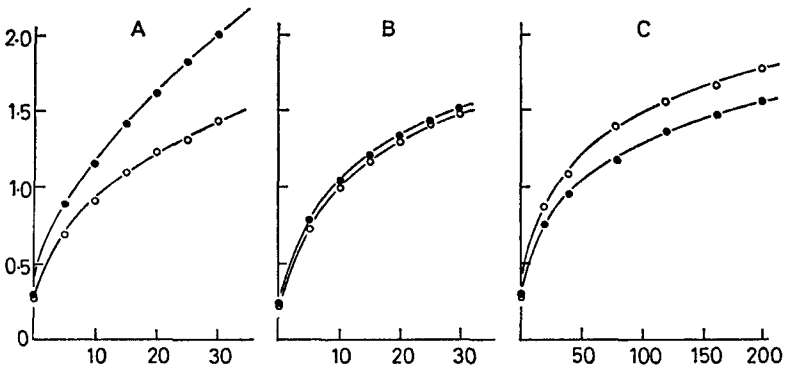

FIG. 1. Heckel plots showing the effect of die size and mode of compact dimensional measurement on the compaction behaviour of two grades of microfine cellulose powder (Elcema). A, 10 mm die; compact dimensions measured at pressure. B, 45 mm die; compact dimensions measured at pressure. C, 10 mm die; compact dimensions measured after release and elastic and strain recovery. ○ = Elcema P050 ● = Elcema P 100. Ordinate: ln $1/(1-\rho_f)$. Abscissa: applied pressure (MN m^{-2})

between materials. The values however, will not be universally applicable for all experimental conditions for the reasons discussed above. Nevertheless a generalized qualitative classification distinguishing types of compaction behaviour can be made (Hersey & Rees 1971; York & Pilpel 1973) which has been found useful in several studies of pharmaceutical powders, simple mixtures and multicomponent formulations (Esezebo & Pilpel 1978; Kurup & Pilpel 1978; York 1978).

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REFERENCES

Bockstiegel, G. (1972) in: Goldberg, A. S. (ed.) Proceedings of the First International Conference on the Compaction and Consolidation of Particulate Matter. Brighton, October 1972. Powder Advisory Centre, London, 1973.

Cole, E. T., Rees, J. E., Hersey, J. A. (1975) Rheol. Acta 50: 28–32

Cooper, A. R., Eaton, L. E. (1962) J. Am. Ceram. Soc. 45: 97–101

De Blaey, C. J., Polderman, J. (1970) Pharm. Weekbl. 105: 241–250

De Blaey, C. J., Polderman, J. (1972) Ibid. 106: 57–65

Esezebo, S., Pilpel, N. (1978) J. Pharm. Pharmacol. 29: 75–81

Fell, J. T., Newton, J. M. (1971) J. Pharm. Sci. 60: 1866–1869

Hardman, J. S., Lilley, B. A. (1970) Nature (London) 228: 353–355

Heckel, R. W. (1961) Trans. Metall. Soc. A.I.M.E. 221: 671–675

Hersey, J. A., Rees, J. E. (1970) Second Particle Size Analysis Conference, Society for Analytical Chemistry, Bradford 1970

Hersey, J. A., Rees, J. E. (1971) Nature (London) 230: 96

Hersey, J. A., Cole, E. T., Rees, J. E. (1972) in: Goldberg, A. S. (ed.) Proceedings of the First International Conference on the Compaction and Consolidation of Particulate Matter. Brighton, October 1972. Powder Advisory Centre, London, 1973.

Jones, T. M. (1977) in: Polderman, J. (ed.) Formulation and Preparation of Dosage Forms. Elsevier, North-Holland, p. 40

Kurup, T. R. R., Pilpel, N. (1978). Powder Technol. 19: 147–155

Rue, P., Rees, J. E. (1978) J. Pharm. Pharmacol. 30: 462–463

Walker, E. E. (1923) Trans. Faraday Soc. 19: 17–82

York, P. (1978) J. Pharm. Pharmacol. 30: 6–10

York, P., Baily, E. (1977) Ibid. 29: 70–74

York, P., Pilpel, N. (1973) Ibid. 25: 1P–11P

The effect of neuroleptic drugs on serum and cerebrospinal fluid melatonin concentrations in psychiatric subjects

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The role of the pineal gland in normal physiology and in pathophysiological conditions is little understood. The active metabolite is thought to exert an inhibitory action on the pituitary-gonadal axis (Minneman & Wurtman 1975) and also to control cyclic variations in sleep and arousal (Quay 1974). We have recently established (Smith et al 1977b) a diurnal rhythm in normal human blood melatonin (MT) measured by radioimmunoassay (RIA) which is synchronous with human post mortem pineal synthetic enzymes where maximal and minimum values occurred around 0200 h and 1400 h respectively. The pineal gland has for two centuries been implicated in psychiatry, the evidence being recently reviewed by (Mullen & Silman 1977). In preliminary studies (Smith et al 1977a), we reported blood MT concentrations in psychiatric subjects. The results fell into two groups, those with high MT concentrations and little rhythm and those with very low MT concentrations, and hardly any rhythm. We suggested that the high level group correlated with those subjects being treated with chlorpromazine (CPZ). In an extension of these studies, we now confirm that chlorpromazine does indeed increase serum but not c.s.f. MT concentrations. Furthermore, the effect appears to be dose related. We also comment on the effect of other neuroleptic drugs.

Blood samples (10 ml) were collected at 4-hourly intervals for 24 h from normal and psychiatric subjects. Subjects were awakened from sleep in a dark room for night sampling. Serum (1 ml) and 2 M phosphate buffer (pH 10·1 1·5 ml) saturated with potassium chloride were extracted with 15 ml light petroleum (b.p. 40–60 °C), the aqueous phase was then extracted with chloroform (25 ml) (redistilled), and the organic phase evaporated under nitrogen at 37 °C. The residue was taken up in ethanol (1 ml) and transferred to the assay tube. The solvent was evaporated again under nitrogen at 37 °C and the MT measured by RIA as described by Arendt et al (1975). The antibody (raised in rabbits by the method of Arendt et al 1975) is specific for MT, exhibits no serious cross reaction with any of the major indoles, including 6-hydroxy-MT and *N*-acetyl-5-hydroxytryptamine, and is sensitive to 10 pg ml^{-1} of serum. The final antibody dilution is 150:1. Interassay and intra-assay coefficients of variation are 16 and 11% respectively. All glassware

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