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COMMUNICATIONS

The prediction of paracetamol capping tendencies

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Numerous materials exhibit capping (the separation of the crown from the remainder of the tablet) during or after a tableting operation. Although paracetamol is the most widely studied powder that is prone to capping, the precise mechanism of capping in paracetamol and its granulations has not been fully elucidated. Shotton & Ganderton (1961) attributed capping to strong interparticulate bonding which results in failure under recovery stresses that propagate across grains. However, more recent research has attributed capping in paracetamol tablets to a low degree of plastic flow and bonding, as measured by residual die wall pressure (Obiorah & Shotton 1976; Doelker & Shotton 1977) or brittle fracture propensity (Hiestand et al 1977). This conclusion suggests that strong interparticulate bonding would eliminate, rather than cause capping.

As early as 1963, Milosovich postulated that capping was due to the expansion of elastically deformed particles and the subsequent rupture of interparticulate bonds. This idea was supported by the observation that capping occurs in a peripheral ring parallel and near to the upper punch surface i.e. at the points of greatest pressure and elastic deformation. Carless & Leigh (1974) showed that the granulation of paracetamol with binders that eliminated capping resulted in both an increase in residual die wall pressure and a decrease in elastic recovery. Ritter & Sucker (1980) similarly concluded that capping tendencies for a mixture of Avicel PH-102 (99%) and magnesium stearate (1%) were dependent on the relative magnitudes of interparticulate bonding and elastic particle deformation. Gregory (1962) attributed laminate failure in coal briquettes to the entrapment of gases, however, it has been shown for hexamine (Shotton & Ganderton 1961) and phenazone mixtures (Ritter & Sucker 1980) that compaction in a vacuum does not effect capping tendencies.

The aim of this study is to investigate the effects of interpariculate bonding and elastic particle deformation on capping tendencies in paracetamol tablets. With an understanding of the major factors causing capping, quantitative predication of the capping tendencies of various formulations when tableted should be possible.

Table 1. Caping indices (C_i).

Paracetamol formulation	C_i (%/MPa)
Crystals	7·1
APOC	1·1
DC	0·53

Methods

Three paracetamol formulations, namely, paracetamol crystals (Graessar Salicylates), Paracetamol DC (Nicholas) and paracetamol APOC granules (Ho & Hersey 1980; Krycer & Hersey 1981) were employed. All powders were sized between 125 and 180 μm and oven dried at 60 °C. To minimize the deleterious effects

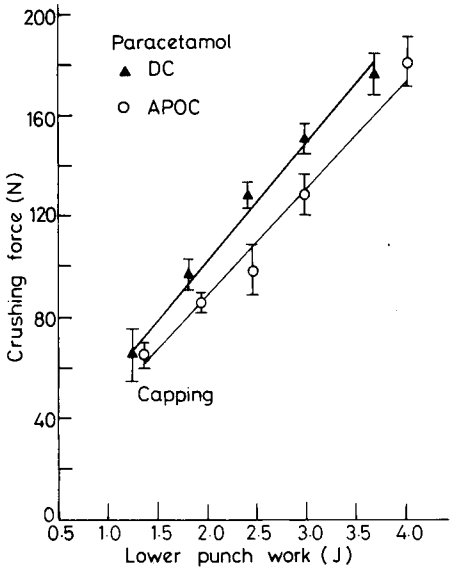

FIG. 1. Energy hardness profiles for paracetamol DC and paracetamol APOC granules. Paracetamol crystals compacted to form extremely weak tablets or tablets that exhibited capping on ejection. Error bars represent 1 standard deviation (n = 5).

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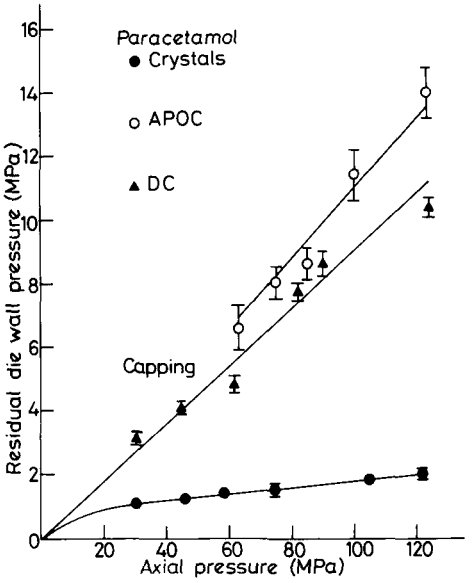

FIG. 2. Residual die wall pressure versus axial pressure for paracetamol crystals and granules after compaction. Error bars represent 1 standard deviation (n = 5).

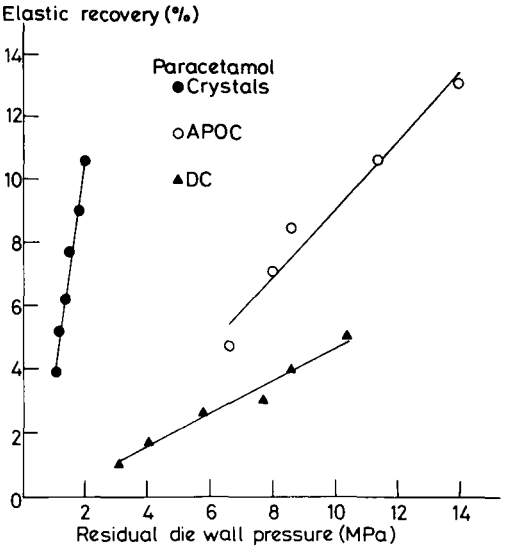

FIG. 3. Percentage elastic recovery versus residual die wall pressure for non-capped tablets of paracetamol crystals and granules.

of lubricants on compact strength, compression was conducted manually with an instrumented Manesty F3 single punch tablet machine. The die wall and upper and lower punch surfaces were lubricated with a 1% suspension of magnesium stearate in acetone. Hand filling of the die with 488 mg of powder was conducted after evaporation of the acetone. Tablet testing was conducted 24 h after compression to allow for full elastic recovery. Crushing strength was determined with a Shleuniger (Model 7410) tablet strength tester. Tablet thickness after ejection was measured with a dial gauge (Mituyo) graduated in 10^{-3} inch divisions.

Results and discussion

Fig. 1 presents energy/strength profiles (Krycer et al 1982) of the two paracetamol granulations employed in this study. Paracetamol crystals are not included as tablets made from this material were either too weak to register on the tablet strength tester or capped on ejection. It is apparent that paracetamol DC utilizes the least energy in the production of strong tablets. Additionally, capping was not encountered with the DC formulation but did occur at low energies of compaction with the APOC granule compacts.

To investigate the extent of plastic flow and subsequent bonding that the compact has undergone during compression, residual die wall pressure (RDWP) measurements were taken. Fig. 2 presents RDWP data for the paracetamol crystals and granules. In this instance axial pressure was correlated with RDWP rather than energy of compaction as the former relates directly to the radial/axial pressure cycle from which RDWP is derived. It is apparent that capping tendencies cannot be predicted solely from RDWP values as the APOC granules exhibit the greatest extent of plastic flow and bonding but still have a tendency to cap (Fig. 2).

To measure the disruptive effects of elastic deformation on a compact, percentage elastic recovery (E) defined by

$$E = 100 \times \frac{H - H_c}{H_c} \quad (1)$$

where H_c and H are the heights of the compact under pressure and after 24 h respectively, was employed. Elastic recovery data were obtainable for paracetamol tablets for although the tablets were extremely weak it was possible to monitor their thickness. A plot of E versus RDWP (Fig. 3) demonstrates that the relative magnitudes of elastic deformation and plastic flow and bonding, determine tablet strength and capping tendencies. Since a tablet must be formed before the determination of E is possible, these plots do not pass through the origin. A capping index (C_i) defined as the gradient of the E versus RDWP plot (Fig. 3), can be employed to quantify tablet capping tendencies. Table 1 presents C_i data for the crystals and granules under investigation. From C_i determinations, predictions of both capping tendencies and the relative tablet strength of various paracetamol formulations are possible. A relatively low C_i value would indicate an absence of capping tendencies and a superior energy utilization in the production of strong tablets. Although only one compound, namely paracetamol, has been used in this study, C_i determinations would also be applicable to other materials that cap by the same mechanism. However, in circumstances

that result in capping by other mechanisms, e.g. capping due to excessive die wall friction, C_i values may not be realistic.

REFERENCES

Carless, J. E., Leigh, S. (1974) J. Pharm. Pharmacol. 26: 289–297

Doelker, E., Shotton, E. (1977) Ibid 29: 193–198

Gregory, H. R. (1962) Trans. Inst. Chem. Engrs. 40: 241–251

Hiestand, E. N., Wells, J. E., Peot, C. B., Ochs, J. F. (1977) J. Pharm. Sci. 66: 510–519

Ho, T., Hersey, J. A. (1980) J. Pharm. Pharmacol. 32: 160–166

Krycer, I., Hersey, J. A. (1981) Powder Technol. 28: 91–95

Krycer, I., Pope, D. G., Hersey, J. A. (1982) The Interpretation of Powder Compaction Data—A Critical Review. Drug Dev. Ind. Pharm. 8: 307–342

Milosovich, G. (1963) Drug Cosmet. Ind. 92 (5): 557–558 and 656: 662–632

Obiorah, B. A., Shotton, E. (1976) J. Pharm. Pharmacol. 28: 629–632

Ritter, A., Sucker, H. B. (1980) Pharm. Tech. Int. July: 25–33, 54

Shotton, E., Ganderton, D. (1961) J. Pharm. Pharmacol. 13: Suppl. 144T–151T.

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Photoactivity of coal tar preparations on microorganisms and DNA

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Coal tar and ultraviolet light have been used in the phototherapy of psoriasis for over 50 years (Goeckerman 1925) but the mode of action remains unclear. The 'synthesis' of DNA in mouse epidermis is inhibited by this form of photochemotherapy (Stoughton et al 1978; Walter et al 1978). Moreover, the formation of DNA interstrand crosslinks similar to those formed with 8-methoxypsoralen (8-MOP) and UVA (320–400 nm) (Scott et al 1976; Song & Tapley 1979) have been reported with coal tar and UVA (Pathak & Biswas 1977). We now report that although we have demonstrated phototoxic activity of coal tar preparations against bacteria and yeasts we were unable to demonstrate the formation of DNA crosslinks with isolated calf thymus DNA.

Materials and methods

The method of Daniels was used for phototoxicity assays with bacteria and yeasts (Towers et al 1977). Briefly, agar plates are spread with living *Candida albicans*. Putative photosensitizers are dried on discs of filter paper, which are added to the plates. One set of plates is incubated in the dark and the other in longwave u.v. light. Phototoxic compounds are those which cause a halo of growth inhibition after incubation in near u.v. (300–400 nm) but not after incubation in the dark.

Calf thymus DNA (Type I, Na salt, Sigma Chemical Co., St Louis, U.S.A.) was dissolved in sodium phosphate butter (0·02 M total phosphate concentration), pH 6·5. DNA solutions were diluted to obtain an absorbance of 2·0 at 260 nm. Two ml of the solutions were mixed with the appropriate compound in plastic dishes (35 × 100 mm style) with lids. The mixtures were shaken under a bank of four Sylvania or Westinghouse black light blue fluorescent bulbs (F20T12-BLB) for 3 h at 23–29 °C. A dark control dish was wrapped in aluminium foil. The intensity of radiation at 360 nm was 2 mW cm^{-2} when measured with an IL 700 radiometer (International Light, Inc.).

Three coal tar preparations were tested for the production of crosslinks in DNA. These were a tar distillate (Doak Pharmacal Co., Inc., Westbury, N.Y.), an oil (Doak Oil, which contains 10% Doak tar distillate in mineral oil) and a coal tar preparation from Currie Products Ltd, Hamilton, Ontario, Canada. 8-MOP (Sigma Chemical Co.) was also tested. The amounts tested were: tar distillate—100 µl, oil—500 µl; coal tar—5 µl of a suspension in benzene (40 mg ml^{-1}), 8-MOP 10 µg (3·3 µl at 3 mg ml^{-1} in 95% ethanol).

The method which we used to detect crosslinks in DNA is similar to that of Cole (1970). DNA solutions were irradiated, transferred to test tubes, heated for 10 min (100 °C) and placed in an ice bath for 5 min. This procedure denatures native DNA but allows renaturation of crosslinked DNA. The DNA solutions were chromatographed on a column of 3 g of hydroxylapatite (Bio-Rad Laboratories, Richmond, CA, U.S.A.). Solutions were applied to the column at a flow rate of 1 ml min^{-1} in this order, (1) the DNA sample, (2) 8 ml of 0·02 M phosphate buffer and (3) a linear gradient (200 ml) of 0·02–0·6 M phosphate buffer. DNA with crosslinks (i.e., renatured DNA) and denatured DNA were separated by the gradient. Fractions of 70 drops (3·6 ml) were collected and their absorbance at 260 nm was measured.

Results

Phototoxicity results are presented in Table 1. The tar distillate was phototoxic for all organisms tested except *Streptococcus faecalis*. Doak oil was phototoxic to all

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