We are grateful to May and Baker Ltd, Dagenham, for the gift of metronidazole.

REFERENCES

Ashton, M. D., Farley, R., Valentin, F. H. H. (1964) J. Sci. Instr. 41: 763–765

Bangudu, A. B., Pilpel, N. (1984) J. Pharm. Pharmacol. 36: 717–722

British Pharmacopoeia (1980) HMSO London, p. 294

Chan, S. Y., Pilpel, N., Cheng, D. C.-H. (1983) Powder Technol. 34: 173–189

Cheng, D. C.-H. (1968) Chem. Eng. Sci. 23: 1405–1420

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

Itiola, O. A. (1986) Ph.D. Thesis, University of London

Itiola, O. A., Pilpel, N. (1986a) Int. J. Pharm. 31: 99–105

Itiola, O. A., Pilpel, N. (1986b) J. Pharm. Pharmacol. 38: 81–86

Kurup, T. R. R., Pilpel, N. (1979) Asian J. Pharm. Sci. 1: 75–90

Martindale, The Extra Pharmacopoeia (1982) 28th Edn, Pharmaceutical Press, London, pp 968–973

J. Pharm. Pharmacol. 1987, 39: 647–650
Communicated January 27, 1987

Determination of the apparent failure viscosity of tablets

C. I. PATEL, J. N. STANIFORTH*, *Particle Engineering Research Group, School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK*

Quantitative differences in the plasticity of several direct compression excipients were found to be distinguishable using normalized work of failure determinations. New parameters were developed to characterize the importance of changes in strain rate application during a diametral crushing test. Failure viscosity was found to have a similar sensitivity to normalized work of failure measurements and was also able to distinguish small changes in plastic behaviour. In cases where it is not possible to measure tablet deformation during tablet crushing, failure viscosity determinations could provide an alternative method for characterizing differences in deformation behaviour.

The tension test was first used for testing pharmaceutical tablets by Newton & Fell (1968), when a tablet was placed along its edge between two flat platens. The deformation undergone by the tablet during diametral testing has been measured by Rees & Rue (1978). The measured deformation of the tablet is not a true tensile strain, but a deformation of the tablet in the direction of compressive loading. Those workers calculated the area under the force applied versus tablet deformation curve and related this parameter to the toughness of the tablet as defined by Dieter (1961). Rees & Rue (1978) termed the calculated area 'work of failure' (WF) which was calculated according to equation 1.

$$WF = \int_0^x F.\,dx \qquad (1)$$

where F is the force applied and x is the tablet deformation.

However WF does not take into account the rate of crack propagation through the tablet prior to failure. It has been recently reported (Patel et al 1987) that the rate of fatigue crack propagation is influenced by the physicomechanical properties of the powder; the latter also governs the degree of interparticle bonding during compaction. One possible parameter that can be derived is the 'power of failure' i.e. the total power expended in causing tensile failure of the tablet, which can be calculated by dividing the work performed to cause tensile failure (WF) by the time of load application. By treating tablets as non-Newtonian plastic solids, another parameter can be derived, 'apparent failure viscosity' (AFV) with units of stress per strain rate (Pas).

Materials and methods

Materials. Anhydrous lactose (Sheffield Chem. Co., USA), Tablettose (Meggle Milchindustrie, GmbH, Reitmehring, FRG), Dipac (Amstar Corp., NY, USA), Nutab (Ingredient Tech. Corp., NJ, USA), Emcompress (Edward Mendell Co., Carmel, USA) and magnesium stearate (BDH Chemicals, Poole, UK) were used.

Methods. Powders to be compressed were stored for 48 h at 25 °C, 55% r.h. before mixing with 1% w/w magnesium stearate and compressed at a compaction rate of 75 tablets min^{-1} to produce tablets each weighing 500 mg. Compressional work was carried out on a single station reciprocating tableting machine (Manesty, type E2, Manesty Ltd, Speke, Liverpool, UK) fitted with strain gauge-instrumented 12·7 mm flat-faced punches. The complete system for tablet compression, including analogue–digital conversion data acquisition and manipulation to determine the force applied during compaction has been fully described elsewhere (Patel 1986). The compressed tablets were stored for 48 h at 25 °C, 55% r.h. before mechanical testing. A tensile tester (type T22K, JJ Lloyd Instr., Southampton, UK) was used for determinations of the tensile strength, NWF values.

$$NWF = \frac{2\pi}{DT} \int_0^x F.\,dx \qquad (2)$$

where NWF is the normalized work of failure, D is the tablet diameter, T is the tablet thickness, F is the force applied and x is the tablet deformation.

* Correspondence.

The power of failure values were calculated by dividing the WF by the time elapsed during the diametral testing of the tablets, the latter was determined using the internal clock of the microprocessor. Apparent failure viscosity of the tablets was calculated by dividing the tensile strength of the tablets by their strain rate, where strain was derived from the deformation undergone by a tablet during the diametral test divided by the tablet diameter and thus on being further divided by the time elapsed during the diametral test to cause tensile failure, gave the strain rate.

Results and discussion

Of all the direct compression excipients examined, Nutab tablets were found to possess the lowest tensile strength (Fig. 1), where the increase in tensile strength with increase in compaction force was found to be lower in comparison with the other excipients, suggesting that there was relatively little influence of compaction force on the degree of interparticle bonding for Nutab. Anydrous lactose and Fast-Flo tablets were found to possess the highest tensile strengths, but only slightly higher than that of Dipac tablets (Fig. 1). The results suggest that the strength of interparticle bonding was greatest for anhydrous lactose and Fast-Flo, probably due to the higher degree of plastic deformation taking place during tablet compaction and consequently, allowing particles to establish areas of intimate contact over which strong attractive electric forces develop thus resulting in strong interparticle bonding. The tensile strengths of Dipac tablets were found to be only slightly lower than those for Fast-Flo and anhydrous lactose, suggesting that Dipac tablets possessed slightly lower strengths of interparticle bonding. Tablettose and Emcompress tablets were found to possess tensile strengths lower than that for Dipac. A possible reason for the lower tensile strengths is that during compaction of these powders, the major consolidation mechanism is brittle fragmentation, leading to an increase in the number of finer particles (Higuchi et al 1953; Armstrong & Haines-Nutt 1970) with clean new surfaces which enable strong interparticle bonding to take place when particle surfaces are brought in close proximity. However, the increase in fines leads to a reduction in tablet porosity causing an instantaneous increase in the number of interparticle contact points. This has the effect of decreasing the magnitude of the load at each contact point, consequently preventing the particles coming into close proximity and reducing the possibility of the establishment of intimate contact areas.

Schubert et al (1975) have stated that the tensile strength of materials may be identical despite the fact that the materials had different fracture strains. The deformation undergone by tablets prepared from various direct compression excipients during diametral tensile testing is illustrated in Fig. 2. There are two general types of behaviour which can be determined from the relationship shown in Fig. 2. Type 1 behaviour

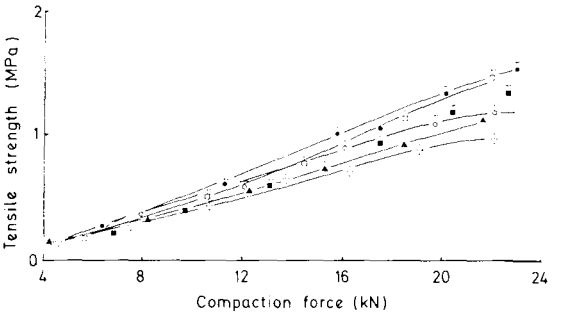

FIG. 1. Relationship between tablet tensile strength and compaction force for some direct compression excipients: (●) anhydrous lactose, (□) Fast-Flo, (■) Dipac, (▲) Emcompress, (○) Tablettose, (▽) Nutab. Tensile strength values plotted are the means of ten determinations and the corresponding confidence interval at 95%.

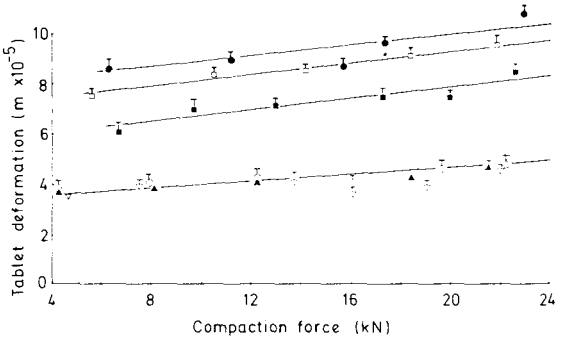

FIG. 2. Relationship between tablet deformation during diametral testing and compaction force for some direct compression excipients: (●) anhydrous lactose, (□) Fast-Flo, (■) Dipac, (▲) Emcompress, (○) Tablettose, (▽) Nutab.

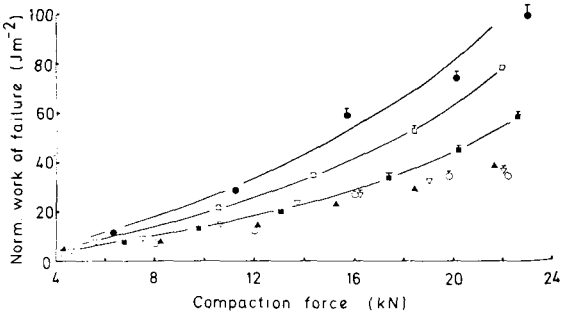

FIG. 3. Relationship between normalized work of failure and compaction force for some direct compression excipients: (●) anhydrous lactose, (□) Fast-Flo, (■) Dipac, (▲) Emcompress, (○) Tablettose, (▽) Nutab.

was found in specimens where the 'fracture strain' at the lowest compaction force is small. Type 1 behaviour was observed with Nutab, Tablettose and Emcompress tablets. Type 2 behaviour is characterized by an increase in tablet deformation with increase in compaction force

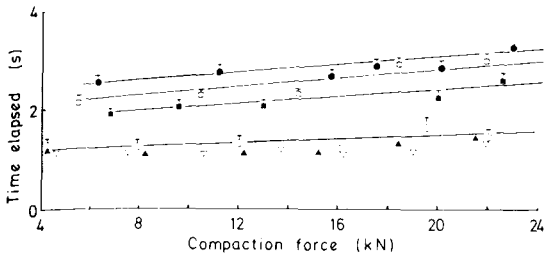

FIG. 4. Relationship between the time elapsed during diametral testing of tablets and compaction force for some direct compression excipients: (●) anhydrous lactose, (□) Fast-Flo, (■) Dipac, (▲) Emcompress, (○) Tablettose, (▽) Nutab.

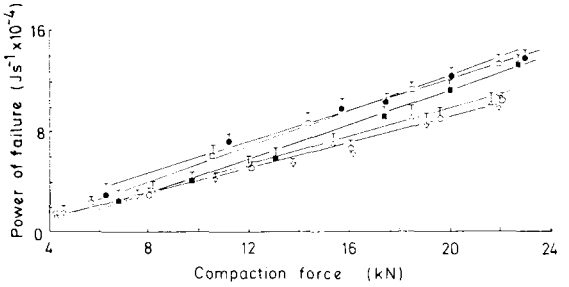

FIG. 5. Relationship between the power of failure of tablets and compaction force for some direct compression excipients: (●) anhydrous lactose, (□) Fast-Flo, (■) Dipac, (△) Emcompress, (○) Tablettose and (▽) Nutab.

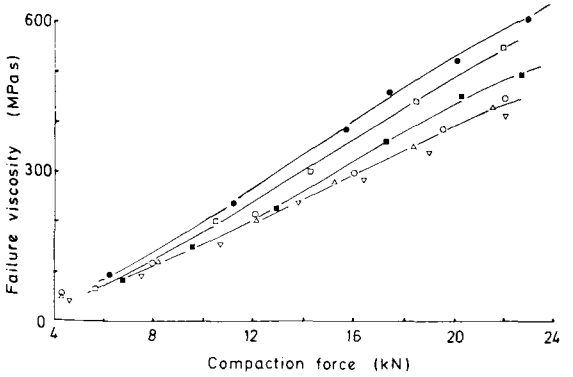

FIG. 6. Relationship between failure viscosity and compaction force for some commercial direct compression excipients. (●) anhydrous lactose, (□) Fast-Flo, (■) Dipac, (○) Tablettose, (△) Emcompress and (▽) Nutab.

and where the 'fracture strain' at the lowest compaction force is greater than that found in type 1 behaviour. Anhydrous lactose, Fast-Flo and Dipac were found to exhibit type 2 behaviour. Rees & Rue (1978) also observed that this type of behaviour difference was undetectable using tensile strength determination and those workers derived a different parameter, work of failure. Tablettose, Nutab and Emcompress were found to possess the lowest normalized work of failure (NWF), anhydrous lactose tablets were found to possess the largest NWF, with Fast-Flo and Dipac tablets having intermediate values. Whereas the tensile strengths of anhydrous lactose and Fast-Flo tablets were previously found to be similar (Fig. 1), their NWF values were disparate (Fig. 3) exemplifying the concern expressed by Schubert et al (1975) over the sole use of tensile strength data to characterize mechanical properties of materials. The difference in tensile strength and NWF values results from differences in tablet deformation (Fig. 2).

Anhydrous lactose, Fast-Flo and Dipac showed an increase in time elapsed with increase in compaction force (Fig. 4) while time elapsed remained nearly constant for Emcompress, Nutab and Tablettose. Such behaviour could be predicted by studying the tablet deformation plots (Fig. 2) since the rate of platen movement is constant in this study (2 mm min^{-1}). A new parameter was postulated to account for the differences in elapsed time, termed 'power of failure' (J s^{-1}) so as to provide a measure of the power expended in causing tensile failure of tablets. It was hypothesized that such a parameter could be more sensitive to minor changes in plasticity of powders than tensile strength of NWF measurements. However, the power of failure values show (Fig. 5) a distinct lack of sensitivity to powder plasticity especially for anhydrous lactose, Fast-Flo and Dipac, differences which were apparent in NWF-compaction profiles (Fig. 3). Hence the above hypothesis was found to be invalid for the direct compression excipients studied. The deformation which a tablet undergoes during a diametral test gives an indirect indication of the time taken for a crack to propagate through the tablet. Dividing WF, which takes into account tablet deformation, by the time elapsed during a diametral test would obviously lead to a reduction in sensitivity. However, the introduction of a time component into the work term may prove useful industrially as a means of rationalizing tablet strength measurements for quality assurance purposes between equipment which have different rates of platen movement. Under such circumstances, tensile strength or NWF values differ because tablets being subjected to a high strain rate may attain only a small NWF at failure, whereas an identical tablet strained at a slower rate would have a higher NWF. When the time to failure is considered, however, the first tablet's low NWF will be increased whereas the second tablet's NWF will be decreased—the two tablets could therefore have similar power of failure values, thus providing a standard test for different equipment.

Another parameter derived was termed 'apparent failure viscosity' (AFV) and the relationship between AFV and compaction force for some direct compression excipients is illustrated in Fig. 6 and gives a similar classification of the excipients as the NWF-compaction force profiles (Fig. 3). Apparent failure viscosity is a measure of the resistance to deformation offered by the

tablet when subjected to diametral loading. The AFV values will be large when the resistance to flow is high—a situation which arises as a result of formation of a large number of high strength interparticle bonds. These conditions predominate when plastic deformation of the particles takes place during compaction, thus the results suggest that anhydrous lactose possesses higher plasticity than any of the other direct compression excipients studied. Both AFV and NWF determinations were found to be useful parameters for predicting the plasticity of excipients.

Conclusion. It may be concluded that use of NWF determinations allowed quantitative differences in plasticity of some excipients to be distinguished. Failure viscosity used the time component of tablet loading as a multiplier and was therefore found to have a similar sensitivity to changes in excipient plasticity to that obtained using NWF and it was considered that both AFV and NWF determinations gave a good indication of the plasticity of different excipients. It can be concluded that use of a second new parameter termed 'power of failure', developed to take account of differences in crack progagation rates between tablet excipients lacked the sensitivity required to distinguish changes in plastic behaviour, but may provide a useful method of comparing tablet crushing tablet strengths using test equipment with different rates of platen movement.

REFERENCES

Armstrong, N. A., Haines-Nutt, R. F. (1970) J. Pharm. Pharmacol. 22: 85–103

Dieter, G. E. (1961) Mechanical Metallurgy, McGraw-Hill, USA, pp 242–243

Higuchi, T., Tao, A. N., Busse, L. W., Swintowsky, J. V. (1953) J. Am. Pharm. Sci. Ed. 42: 194–200

Newton, J. M., Fell, J. T. (1968) J. Pharm. Pharmacol. 20: 657

Patel, C. I. (1986) Ph.D. Thesis, University of Bath, UK

Patel, C. I., Staniforth, J. N., Lindley, M. (1987) Int. J. Pharm. in press

Rees, J. E., Rue, P. J. (1978) Drug Develop. Ind. Pharm. 4: 157–174

Schubert, H., Herrmann, W., Rumpf, H. (1975) Powder Tech. 11: 12

J. Pharm. Pharmacol. 1987, 39: 650–652
Communicated December 30, 1986

Unloaded polyisobutylcyanoacrylate nanoparticles: efficiency against bloodstream trypanosomes

C. LHERM, P. COUVREUR*, P. LOISEAU†, C. BORIES†, P. GAYRAL†, *Laboratorie de Pharmacie Galénique et de Biopharmacie and †Laboratoire de Parasitologie, Université de Paris XI, Chatenay-Malabry, France*

The potential use of polyisobutylcyanoacrylate nanoparticles in antiparasitic chemotherapy is described. The nanoparticles on their own proved to have trypanocidal activity against *Trypanosoma brucei brucei* in-vitro but not against *Trichomonas vaginalis* or *Entamoeba histolytica*. The trypanocidal activity was partly confirmed in-vivo with *T. brucei*-infected mice.

Previous studies have demonstrated the interest in polyalkylcyanoacrylate nanoparticles as colloidal carriers of drugs (Couvreur et al 1979, 1982). These ultrafine particles, 100–200 nm in size, were shown to be able to entrap in their polymeric network a wide variety of drugs (i.e. cytostatics, antibiotics, hormones), the tissue distributions of which were modified after administration to animals (Couvreur et al 1980; Grislain et al 1983).

Moreover, because of the lack of success in the treatment of third-world endemic parasitic diseases (Meshnick 1984), drug carriers have been considered as a means of achieving a better specificity of commonly used antiparasitic compounds (Alving et al 1980). In view of such a strategy, we have made preliminary experiments to check the toxicity of nanoparticles against different species of parasitic protozoa in-vitro. This paper describes unexpected antiparasitic activity observed with unloaded nanoparticles against *Trypanosoma brucei brucei* both in-vitro and in-vivo.

* Correspondence.

Materials and methods

Isobutylcyanoacrylate monomer was obtained from Ethnor (Paris, France). Various chemicals including dextran 70 and D-glucose were purchased from Prolabo (Paris, France). Culture media and foetal calf serum were from GIBCO (Biocult., Paris, France) and culture plates from Falcon (Grenoble, France). Female mice CD1 (Charles River, Cleon, France) were 18–20 g.

The parasite strain *Trypanosoma b. brucei* (Institut Pasteur, Paris, France), conserved in liquid nitrogen with 10% glycerol as cryoprotectant, was administered to the mice by intraperitoneal injection according to Hawking (1963a).