DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(15-17), 2109-2126 (1988)

THE DEFORMATION OF ALPHA-LACTOSE MONOHYDRATE AND ANHYDROUS ALPHA-LACTOSE MONOCRYSTALS

D Y T Wong, P Wright* and M E Aulton

School of Pharmacy, Leicester Polytechnic, Leicester LE1 9BH, UK
and *Fisons plc, Pharmaceutical Division, Loughborough, Leics LE11 ORH, UK

ABSTRACT

Alpha-lactose monohydrate monocrystals were grown from supersaturated solution in agar gel and the anhydrous form was prepared by refluxing the monohydrate crystals in specially - dried methanol. The compression characteristics of the single crystals were assessed in two ways - by indentation testing and by the use of a novel single-crystal compression rig.

Indentation testing showed that the anhydrous crystals are much softer, less elastic and have a lower resilience than the monohydrate crystals. The anhydrous crystals are also much less anisotropic, i.e. they show greater similarity in the properties of their faces.

The crushing strength rig produced stress - strain data and concurrent photographic evidence of single crystal deformations. The anhydrous crystals withstood a lower maximum recorded load,

exhibited lower displacement prior to destructive cracking and thus required less work to break than the corresponding monohydrate crystal. The monohydrate crystals undergo much more pronounced splitting and fragmentation (spalling) than the anhydrous ones which tend to crush by gradual localised cracking at the point of contact.

Data on the deformation of single crystals can be used to explain observations made on the bulk compression of different types of lactose.

INTRODUCTION

There is an increasing awareness of the need to understand the deformation and bonding characteristics of single particles and crystals and how these properties, in turn, influence the bulk behavioural properties of a compact as a whole (see, for example, Humbert-Oroz et al.[1] and Huttenrauch[2].

The work presented here is part of a study to examine the mechanical behaviour of a range of single crystals of pharmaceutical interest. Specifically, this present work compares the deformation characteristics of monocrystals of alpha-lactose monohydrate and anhydrous alpha-lactose. Lactose, a commonly-used tablet diluent, has advantages for this type of work in that single particles of an easily-manipulatable size can be produced in an amorphous form and in a range of crystalline forms with various crystal habits. The scheme of Vromans et al.[3] summarises the formation of the various solid forms of lactose from solution. In addition, numerous workers, notably Lerk et al.[4], have shown how these various forms of lactose influence bulk multiparticulate performance during tablet compression. They have shown that the anhydrous material behaves differently to the monohydrate during tabletting.

In this present work, alpha-lactose monohydrate monocrystals were grown from supersaturated solution in agar gel and the anhydrous form was prepared by refluxing the monohydrate crystals in specially-dried methanol.

The compression characteristics of the single crystals were assessed in two ways. Firstly by indentation hardness testing using the apparatus and technique described by Aulton, Houghton and Wells[5], and secondly using a novel single-crystal compression rig.

MATERIALS

Lactose monohydrate (Sigma) was used for this work. Monocrystals of alpha-lactose monohydrate were grown by an agar-gel suspension technique (Wong and Aulton)[6]. This consists of forming a saturated solution at 60°C in a 0.7% aqueous agar solution. The solution was cooled to 35°C to gel the agar and the correct supersaturation was achieved by warming to 39°C. This technique ensures that the crystals grow in isolation to form a range of macroscopically well-formed crystal habits and sizes.

The anhydrous crystals were formed by refluxing monohydrate crystals in specially-dried methanol (BDH) (50ml per 1g of crystals) at 64°C for 1 hour. The resulting crystals retained the same macroscopic dimensions as their parent monohydrate crystal but were devoid of water of crystallization and had a more opaque appearance and a rougher surface. The anhydrous crystals are stable at ambient atmospheric conditions.

METHODS

Indentation Testing

A computer-interfaced microindentation apparatus was used. This was developed by Aulton, Houghton and Wells[5] and consists of the ICI pneumatic microindentation apparatus[7] from which the pneumatic amplifier and chart recorder had been removed and replaced with an LVDT system. The core of the transducer is fitted to the beam of the indenter and the body to the static framework. The core moves with the indenter tip allowing accurate quantification of indenter penetration into the crystals. The LVDT output is sent to a modified analogue-to-digital converter in a BBC microcomputer which enables depth versus time profiles to be logged and stored. A suite of software allows manipulation of the data to give indentation paramenters. The apparatus was modified further for the specific needs of single crystal deformation by fitting a universally-jointed stage which allows tilting of the crystal sample in order to allow perpendicular indentation into the many angled faces of the lactose crystals, see Figure 1.

In this work, a load of 30g was lowered onto a spherical indenter of 0.68mm diameter for 150 seconds. Recovery of the indentation after load removal was followed for a further 150 seconds.

Crushing Strength Apparatus

This apparatus (see Figure 2) consists of two platens; one of which is static and is attached to a 50N load transducer (Manwood Instruments, type U4000). The second platen is movable and is driven by a motor at a wide range of possible strain rates

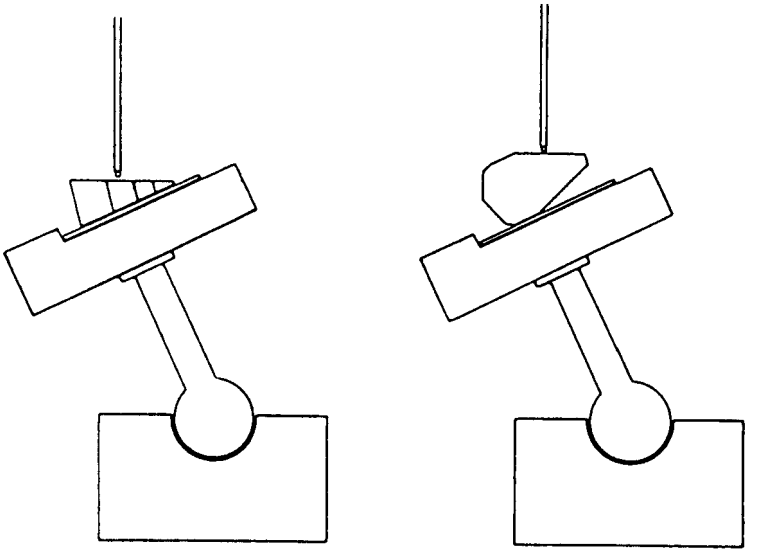

FIGURE 1

Universally-Jointed Crystal Mounting

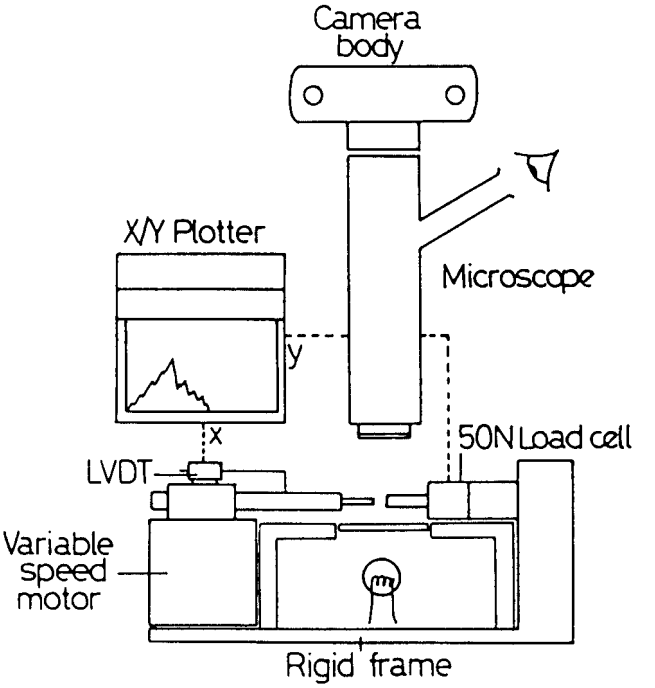

FIGURE 2

The Monocrystal Crushing/Bonding Rig

($13.3\mu m\ s^{-1}$ was used in this work). An interchangeable crystal holder is mounted in the moveable platen. Single crystals, between 1 and 6mm in length, can be mounted on the crystal holder in any desired orientation. As crushing is performed a force-displacement graph is obtained. At the same time the crushing is viewed down a 20x magnification trinocular stereoscopic microscope (Nikon SMZ-10). The sample, illuminated by a twin-beam fibre-optic light source, is photographed through the microscope at regular time intervals by a 35mm SLR camera controlled by a motor drive and time controller (Olympus OM system). The force-displacement curve and concurrent photographic evidence enable the sequence of deformation to be followed. It is also possible to reverse the direction of the motor at any time so that the strength of the bonds so formed can be quantified. Single crystals can also be mounted on the static platen in any desired orientation enabling the study of crystal-to-crystal contacts.

RESULTS

Indentation Results

Table 1 summarises the results of the mechanical properties of the crystals as determined by indentation of specific faces of the crystals. The results for two crystal faces are shown below. The coefficient of variation of the test data is typically between 15% and 20%. Figure 3 defines the Miller indices of alpha-lactose crystals.

The above results show that the anhydrous crystals are much softer, less elastic and have a lower resilience than the monohydrate crystals. The anhydrous crystals are also much less anisotropic, i.e. they show greater similarity in the properties of the two faces tested.

TABLE 1

Mechanical Properties of Monocrystals of Alpha-Lactose Monohydrate and Anhydrous Alpha-Lactose determined by Indentation

Crystal Type	Crystal Face (Miller Index)	Brinell Hardness (MPa)	Elastic Modulus (GPa)	Elastic Quotient	Number of Tests
Alpha-Lactose Monohydrate	(011)	66.7	1.52	0.84	20
	(110)	43.3	0.83	0.80	20
Anhydrous Alpha-Lactose	(011)	29.9	0.87	0.44	30
	(110)	25.6	0.75	0.40	17

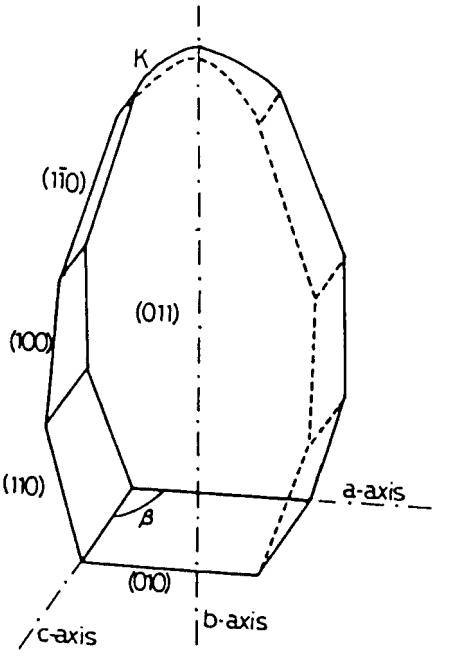

FIGURE 3

Alpha-Lactose Monohydrate Crystal showing Miller Face Indices

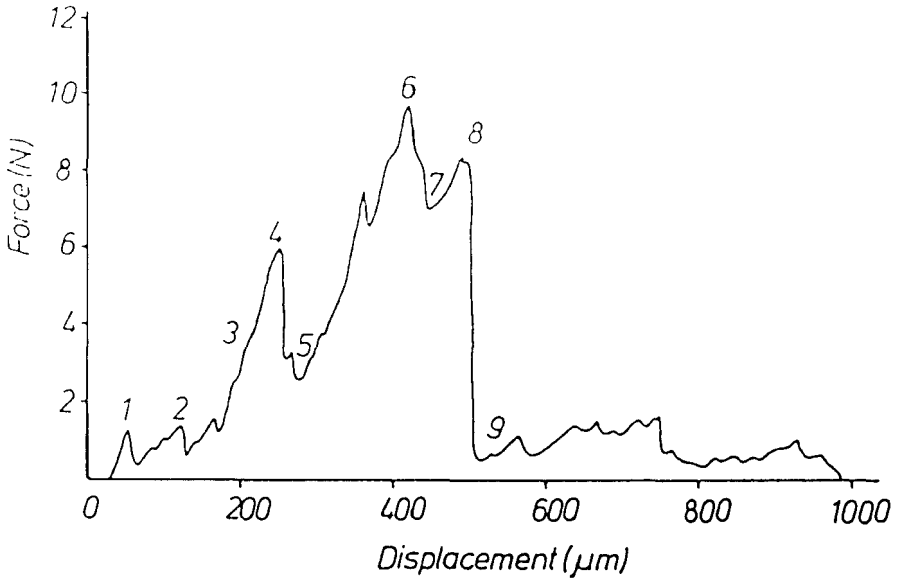

FIGURE 4M

Force versus Displacement Plot During Crushing of an Alpha-Lactose Monohydrate Monocrystal

Crushing Strength Results

The outputs of the LVDT and the load transducer were fed simultaneously to the X and Y axes, respectively, of an XY recorder. The shape of the force-displacement curves obtained from the two types of lactose differed (see Figures 4M (monohydrate) and 4A (anhydrous)). Photographs, which were taken down the microscope at known elapsed time, are presented in Figures 5M (monohydrate) and 5A (anhydrous). The state of the crystal at various points in the force-displacement graphs in Figure 4 can be seen in the corresponding photographs in Figure 5. The position numbers correlate in both figures. The results shown in Figures 4 and 5 are representative of ten replicates.

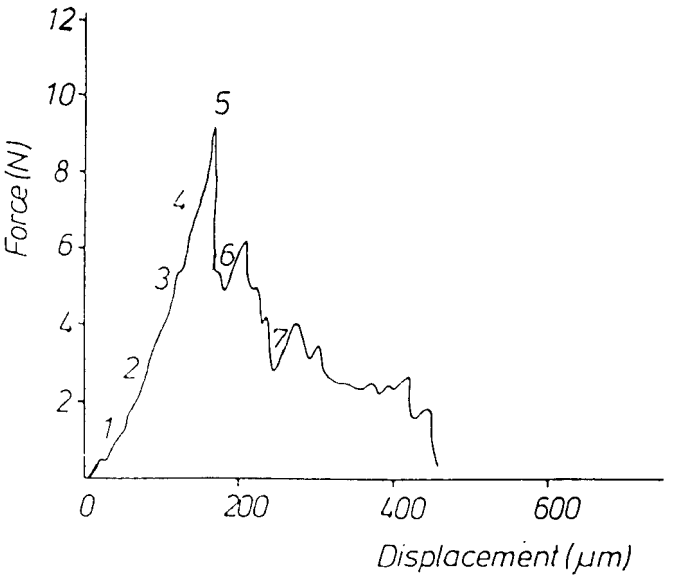

FIGURE 4A

Force versus Displacement Plot During Crushing of an Anhydrous Alpha-Lactose Monocrystal.

Discussion of results

Alpha-Lactose Monohydrate - Figures 4M and 5M

The force-displacement curve for the monohydrate is typically very jagged showing many steep rises and falls. Position 0 is the start point. As the platen holding the crystal in the test rig (on the left in Figure 5) moves towards the static platen, there is - after contact - a resulting increase in stress. The stress rises until it is large enough to produce a crack within the crystal. The stress initially causes cracking at the tip (Position 1). As the stress increases, further internal fractures appear whilst the crystal retains its integrity (Position 2). At Position 3 fragmentation of the

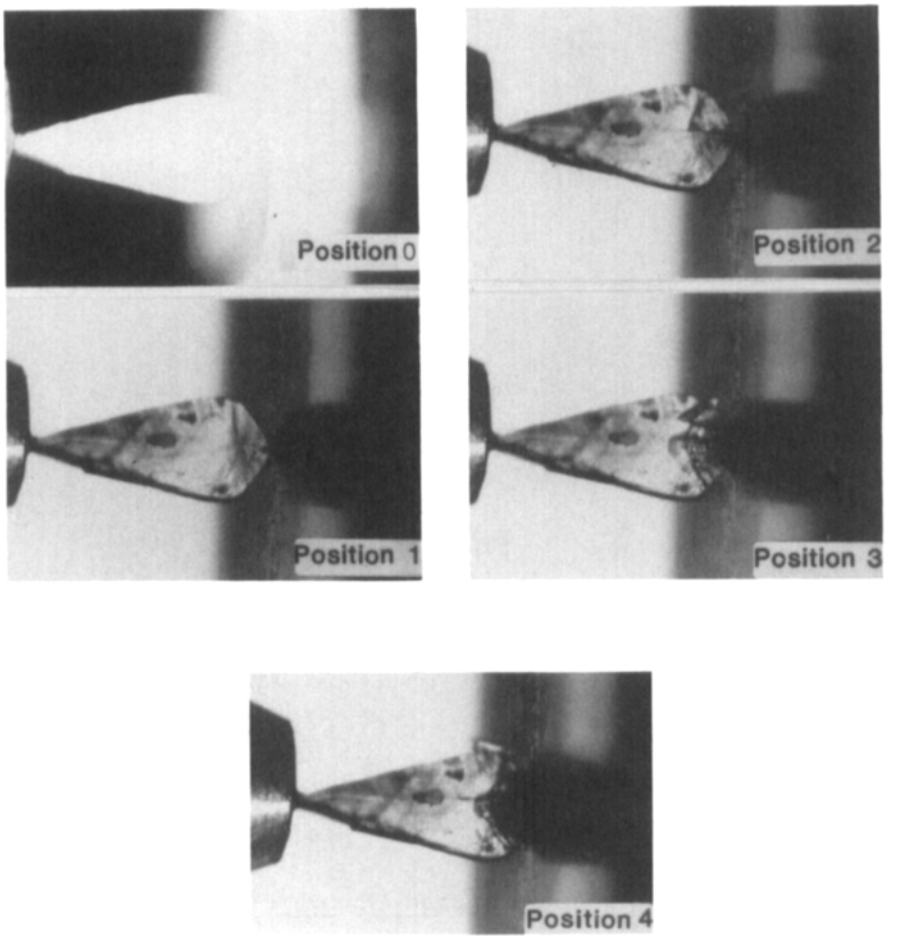

FIGURE 5M

Photographic Sequence of the Crushing of an Alpha-Lactose Monohydrate Monocrystal. The Position numbers correspond to those in Figure 4M.

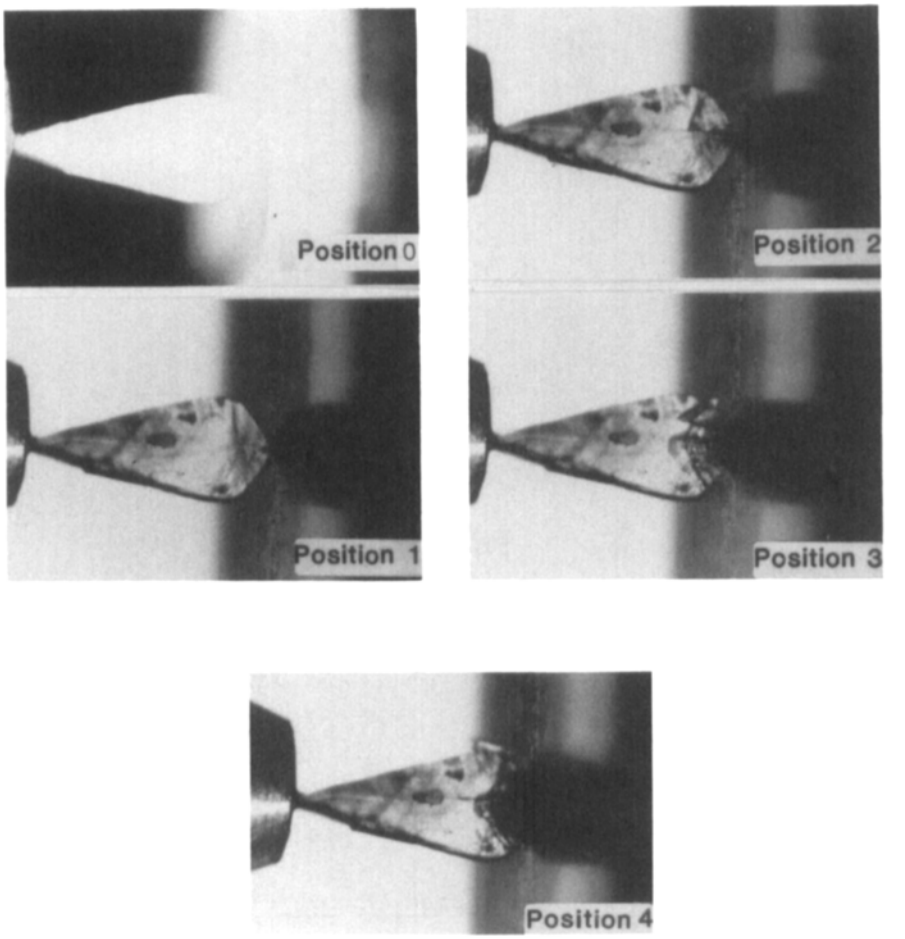

FIG. 5M CONTINUED

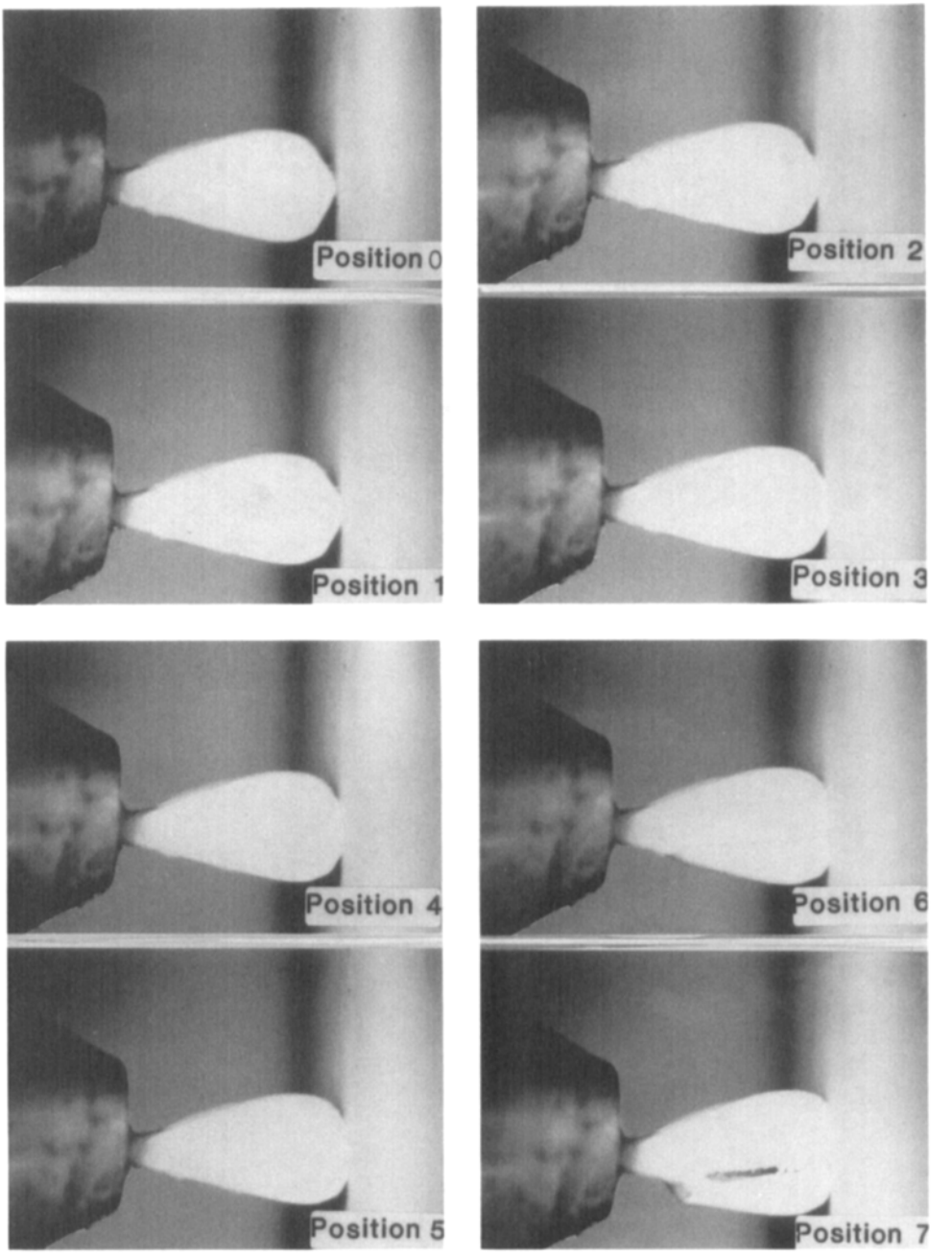

FIGURE 5A

Photographic Sequence of Crushing of an Anhydrous Alpha-Lactose Monocrystal. The Position numbers correspond to those in Figure 4A.

crystal has begun as small flakes of crystal break off. These are so-called spalling cracks and can be clearly seen under the microscope and on the photographic evidence. Fragmentation continues with crack propagation through the crystal, generally in a direction parallel to the (011) face, until a large fracture (see Position 5, Figure 5M) propagates throughout the crystal. This results in a drastic reduction in the force registered (Position 5, Figure 4M). Further compression causes more fragmentation and spalling. A large flake can be seen falling from the main crystal at Position 6 and this resulted in the decrease in recorded force down to Position 7. At the maximum registered force (Position 8) further (terminal) cracking occurs and Position 9 shows the crystal at the point where it has totally collapsed from its mounting giving a low force reading.

Anhydrous Alpha-Lactose - Figures 4A and 5A

The force-displacement curves for the anhydrous crystals were much smoother during load application (Figure 4A). The corresponding photographs show no flaking. The maximum recorded load was lower and the amount of displacement occurring prior to the large destructive crack was less than the corresponding monohydrate crystal.

On following through a typical sequence for the crushing of an anhydrous crystal, Positions 1 to 5 show no obvious internal or spalling cracks. Instead there is loose, brittle fragmentation at the tip of the crystal which crumbles to continually increase the area of contact with the platen. Major fracture occurs at the maximum applied force. The first visible crack does not appear until Position 6 in Figure 5A; the resulting rapid decrease in force is shown in Figure 4A. Position 7 records the widening of this crack and the complete separation of the fragment from the crystal.

TABLE 2

Crushing Strength Data for Monocrystals of Alpha-Lactose Monohydrate and Anhydrous Alpha-Lactose

Property	Alpha-Lactose Monohydrate	Anhydrous Alpha-Lactose
Mean length of crystals tested	3.7mm	4.25mm
Mean width of crystal at base of tip	1.57mm	1.79mm
Cross-sectional area of crystal at base of tip	$0.397mm^2$	$0.498mm^2$
Maximum force recorded (F_{max})	10.32N	9.17N
Maximum stress at base of crystal tip	26.38MPa	19.47MPa
Deflection at F_{max}	303.0μm	237.0μm
% Strain (100 x Δ L/L) at F_{max}	8.8%	5.6%
Work done up to F_{max}	1.650mJ	1.072mJ

Quantitative comparisons

Table 2 records some mechanical properties of the crystals. The results quoted are the mean of 10 readings.

The table shows that the anhydrous crystals withstood a lower maximum recorded load, exhibited a lower displacement prior to the large destructive crack and thus required less work to break than the corresponding monohydrate crystal.

DISCUSSION

The observations and results described above on monocrystals of two types of lactose can be summarised as follows. Alpha-lactose monohydrate crystals are hard, elastic, brittle and strong and compression initiates the progression of large cracks which result in the breaking off of both small and large fragments from the crystals. The anhydrous form, on the other hand, is softer, less elastic and weaker and is deformed by gradual localised crushing of the points of contact of the crystal without large internal cracking or flaking.

These observations do not suggest that the anhydrous crystals are more ductile than monohydrate ones. This term infers an ability to undergo plastic flow. Anhydrous crystals show no plastic flow. The evidence indicates that the anhydrous form is also very brittle but it undergoes brittle fracture much more readily and at lower stresses than the monohydrate.

The indentation data illustrates the anisotropic nature of the mechanical properties of the monohydrate form. This is related fundamentally to the orientation of the crystal planes. In the anhydrous form this anisotrophy is greatly reduced. It

seems that during the dehydration process, the removal of water of crystallisation results in the partial disruption of crystalline order. This disruption could explain the difference in the degree and nature of the fragmentation mechanisms of the two crystal types.

It appears that the less rigid and more isotropic nature of the anhydrous crystals prevent the stress eminating from the points of contact from propagating through the crystal. Instead the anhydrous crystals undergo fragmentation into a large number of very small particles rather than into large splinters as does the monohydrate.

This work provides visual and quantitative confirmation of the bulk compression characteristics for these two types of lactose observed by Bolhuis et al.[8] and Lerk et al.[4II,4III]. They observed superior compression properties of the anhydrous form and related this to and increase in the fragmentability of the anhydrous form as evidenced by an increase in the specific surface area of these materials during tablet compression. This work shows that assumption to be correct.

CONCLUSIONS

The data presented here shows methods that can be used to assess single-crystal mechanical properties. The results were used to explain previous observations made during bulk compression of these two types of lactose. It is envisaged that the data obtained from tests such as these on isolated single crystals will give a much clearer picture of the fundamental deformation and bonding behaviour of pharmaceutical tabletting materials.

ACKNOWLEDGEMENTS

The authors thank Fisons Plc, Pharmaceuticals Division for financial support and Richard Webster for technical assistance.

REFERENCES

1. P. Humbert-Oroz, R. Gurny, D. Mordier and E. Doelker, Int. J. Pharm. Tech. & Prod. Mfr., 4(2), 29-35 (1983).

2. R. Huttenrauch, Pharm. Ind., 45(4), 435-440 (1983).

3. H. Vromans, et al., Proc. Int. Conf. on Pharm. Technol., AGPI, Paris, III, 52-59 (1986).

4. C.R. Lerk, et al. A series of papers entitled "Studies on Tabletting Properties of Lactose" (1985 - 1987). I, Acta Pharm. Suec., 22, 163-172 (1985). II, Pharm. Weekbl. (Sci. Edn), 7, 186-193 (1985). III, ibid, 8, 145-150 (1986). IV, Int. J. Pharmaceut., 28, 229-238 (1986). V, Acta Pharm. Suec., 23, 217-230 (1986). VI, ibid, 23, 231-240 (1986). VII, Int. J. Pharmaceut., 35, 29-37 (1987).

5. M.E. Aulton, R.J. Houghton and J.I. Wells, Proc. 5th Pharm. Technol. Conf., Solid Dosage Research Unit, Harrogate, II, 399 (1985).

6. D.Y.T. Wong and M.E. Aulton, J. Pharm. Pharmacol., 39, Suppl., 124P (1987).

7. C.J.H. Monk and T.A. Wright, J. Oil and Colour Chem. Assoc., 48, 520-528 (1965)

8. G.K. Bolhuis, G. Reichman, C.R. Lerk, H.V. van Kamp and K. Zuurman, Proc. 4th Pharm. Technol. Conf., Solid Dosage Research Unit, Edinburgh, III, 107-130 (1984).