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# Science Papers

# The effect of particle size and shape on the flow and failure properties of procaine penicillin powders

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A study has been made of the effects of particle size and particle shape on the shear and tensile properties of batches of dried procaine penicillin powders whose particle shapes were varied by crystallization from different solvents. The following correlations have been established between the mechanical parameters of the powders and their particle size and shape. $\log C/T = 1{\cdot}706 - 0{\cdot}213 \log (V/S) - 1{\cdot}36\ \alpha_{s.v.a.}$; $(n-1) = 1{\cdot}329 + 0{\cdot}0083\ (V/S) - 0{\cdot}128\ \alpha_{s.v.a.}$; $\tan\Delta = 0{\cdot}812 + 0{\cdot}0057\ (V/S) + 0{\cdot}025\ \alpha_{s.v.a.}$; $FF = 6{\cdot}52 + 0{\cdot}434\ (V/S) - 0{\cdot}528\ \alpha_{s.v.a.}$ The findings are discussed in relation to the design of filling equipment for unit doses of penicillin.

Procaine penicillin is used extensively in therapy and is usually filled into single dose containers through gravity hoppers fitted with auger screw feeders. Control must be exercised over the flow properties of the material if the dose in each container is to conform to the weight limits of the British Pharmacopoeia specifications.

It has been shown previously (Ashton, Cheng & others, 1965; Walton, 1973) that the flow properties of procaine penicillin, like those of other powders, depend on a number of variables. They include intrinsic properties of the powder such as its density and particle size (Farley & Valentin, 1967), but also depend on the degree of consolidation, moisture content etc. (Walton & Pilpel, 1972).

It is now generally accepted that shear tests and tensile tests, made on consolidated beds of the powder are useful, and yield parameters of the powder which have fundamental significance (Jenike, 1961, 1964; Williams & Birks, 1967).

Although work has now been done on the way in which particle size and size distribution affect the values of these parameters (Farley & Valentin, 1967; Cheng, 1968; Kočova & Pilpel, 1972), comparatively little has been published on the particular effects of particle shape (Farley & Valentin, 1967).

This is because it is normally difficult to produce a powder in batches with widely differing particle shapes and with the shapes in any one batch all identical. The problem is only partially overcome by such methods as crystallization, precipitation or micronizing under carefully controlled conditions and there is still no known way of mechanically separating powders into fractions on the basis of their shape, if the particles are smaller than 200 $\mu$m in diameter (Ridgway & Rupp, 1969). Under the circumstances, it is only possible to observe the average shape in an assembly of particles, and several methods for doing this have been described in the literature, together with their relative advantages and disadvantages (Treasure, 1966).

In the present work, we have used the method due to Heywood (1954, 1963) in which an average particle shape is obtained by dividing a so-called "surface coefficient" $K_{sa}$ by a volume coefficient $K_{va}$, these coefficients being obtained by combining Coulter Counting with optical microscopy and measurements of surface area, using an air permeability method.

Procaine penicillin was selected as a useful material for the investigation because it is important industrially and because it can also be prepared in a variety of shapes by controlling the conditions under which it is precipitated from solvents.

The objective of the work was to measure the shear and tensile properties of different batches of the penicillin to see whether correlations could be established between the shapes and sizes of the particles and certain fundamental parameters of the powders which can be used to describe their flow and failure properties in filling equipment.

## MATERIALS AND METHODS

### *Preparation and characterization of penicillin*

Batches of B.P. procaine penicillin with different crystalline shapes were prepared by pouring hot saturated solutions of the material (in methanol, dimethyl acetamide, or a 50:50 mixture of methanol and acetone) into an excess of ice cold water and dried under vacuum at 55°. Analysis showed that no detectable change had occurred in chemical composition and that residual solvents in the penicillin were less than 0·05%, w/w. The batches were separated into narrow size fractions (as judged by optical microscopy) using a Bahco classifier and the size distribution in each fraction was measured on a model A Coulter Counter.

Heywood shape coefficients (1954, 1963), defined by the expression: $\alpha_{s.v.a.,} = K_{s.a.}/K_{v.a.}$ were estimated for each fraction, the shapes in all cases being angular prismoidal. $K_{s.a.}$ is the particle surface coefficient, equal to $S/d_a^2$; $K_{v.a.}$ is the particle volume coefficient equal to $V/d_a^3$; $d_a$ is the mean particle projected diameter and its value was obtained by photographing about 200 particles from each batch at a magnification $\times 700$ and then cutting out and weighing each image. $d_a$ was calculated from the weight per unit area of the photographic paper. The values of S (the mean particle surface area) were obtained from air permeability measurements, using a modified Fisher apparatus (Edmundson, 1966) and knowledge of the number of particles per gram, obtained from the Coulter counter analysis. V is the mean particle volume, calculated from the particle density and the number of particles per gram.

### *Tensile and shear tests*

These were carried out in a controlled atmosphere of less than 20% R.H. at room temperature on samples which had been stored for some weeks over phosphorus pentoxide and whose moisture contents, as measured by Karl Fischer at the time of the tests, were between 2·9 and 3·2% w/w. This corresponds to the procaine penicillin monohydrate. The amount of moisture absorbed during testing was too small to be detected.

The tensile strengths were measured in a tester which has been fully described (Ashton, Farley & Valentin, 1964). Measurements were made after consolidating the powders to different packing densities using a normal load and a twisting action, one sample from each fraction being used throughout because of the small amount

of material available. The samples were de-aggregated by passing through a 200 mesh sieve before testing. There was no evidence that any change occurred in the particle shape or size distribution during the tests. The packing densities were calculated from the measured particle density and the weight and volume of powder in the test apparatus. Shear tests were made in an annular shear cell, whose design and method of operation have also been fully described (Carr & Walker, 1967; Kočova & Pilpel, 1972).

With this apparatus it was possible to obtain the complete family of yield loci on a single sample and to prevent moisture being absorbed during the measurements.

## RESULTS

The results of the shape analyses are given in Table 1.

It is evident that although precipitation from the different solvents had produced batches with different average particle shapes, the shape coefficients in these batches

Table 1. *Surface, volume and shape coefficients and range of interparticle forces.*

| Fraction | Mean particle diameter ($d_a$) $\mu$m | Surface coefficient $K_{s.a.}$ | Volume coefficient $K_{v.a.}$ | Shape coefficient $\alpha_{s.v.a.}$ | Range $t_o$ $\mu$m |
|---|---|---|---|---|---|
| 1a | 27·9 | 3·84 | 0·383 | 10·03 | 0·82 |
| b | 19·2 | 4·33 | 0·552 | 8·27 | 0·82 |
| c | 9·1 | 3·45 | 0·485 | 7·13 | 1·08 |
| 2a | 9·0 | 2·43 | 0·260 | 9·30 | 0·82 |
| b | 3·9 | 2·08 | 0·196 | 10·06 | 0·82 |
| 3a | 19·7 | 6·25 | 0·612 | 10·21 | — |
| b | 14·4 | 3·99 | 0·441 | 9·04 | 0·82 |
| c | 7·2 | 2·46 | 0·232 | 10·06 | 0·82 |
| d | 5·1 | 2·49 | 0·280 | 8·86 | 0·82 |
| 4a | 17·9 | 3·31 | 0·370 | 8·93 | — |
| b | 15·6 | 2·64 | 0·299 | 8·82 | 1·08 |
| c | 9·1 | 2·05 | 0·264 | 7·76 | 1·08 |
| 5a | 17·2 | 3·25 | 0·389 | 8·35 | 0·97 |
| b | 11·5 | 2·37 | 0·270 | 8·78 | 0·97 |
| c | 5·2 | 2·27 | 0·307 | 7·38 | 0·97 |

Fraction 1, by precipitation from 50 : 50 methanol–acetone.
Fraction 2, by precipitation from dimethylacetamide.
Fraction 3, by precipitation from methanol.
Fraction 4, and Fraction 5, commercial samples.

tended to decrease with decrease in particle size and there was also some variation in both shape and size in each fraction of powder tested. This was ascribed to the limitations of the classifier employed.

*Tensile strengths*

The values of the tensile strengths of the fractions at different packing densities are given in Table 2. On plotting the results, it was found that the graphs conform to the well known equation (Ashton & others, 1965)

$$T = K\left(\frac{\rho}{\rho s}\right)^m \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where m and K are constants.

Table 2. *Summary of shear test results*

| Sample | P.D. | T g cm$^{-1}$ | C g cm$^{-1}$ | n | tan$\Lambda$ | FF |
|---|---|---|---|---|---|---|
| | 0·499 | 0·460 | 1·12 | | | |
| | 0·465 | 1·14 | 1·79 | | | |
| 1a | 0·469 | 1·49 | 2·95 | 1·14 | 1·16 | 5·81 |
| | 0·483 | 3·28 | 4·52 | | | |
| | 0·484 | 3·71 | 4·81 | | | |
| | 0·481 | 0·73 | 1·32 | | | |
| 1b | 0·493 | 1·69 | 3·04 | 1·20 | 1·06 | 4·76 |
| | 0·504 | 3·43 | 4·51 | | | |
| | 0·488 | 0·71 | 2·42 | | | |
| 1c | 0·515 | 1·10 | 2·83 | 1·65 | 1·06 | 3·76 |
| | 0·525 | 1·32 | 3·62 | | | |
| | 0·544 | 1·76 | 4·12 | | | |
| | 0·360 | 1·44 | 2·38 | | | |
| | 0·382 | 2·13 | 4·46 | | | |
| 2b | 0·410 | 3·23 | 7·07 | 1·25 | 1·09 | 2·57 |
| | 0·427 | 4·33 | 8·08 | | | |
| | 0·439 | 5·19 | 9·90 | | | |
| | 0·436 | 2·49 | 2·09 | | | |
| | 0·446 | 3·15 | 3·63 | | | |
| 3b | 0·451 | 3·51 | 4·23 | 1·06 | 1·09 | 4·76 |
| | 0·458 | 4·06 | 5·02 | | | |
| | 0·461 | 4·41 | 7·04 | | | |
| | 0·398 | 2·16 | 2·82 | | | |
| | 0·416 | 3·08 | 5·44 | | | |
| 3c | 0·432 | 4·19 | 7·02 | 1·19 | 1·09 | 2·00 |
| | 0·445 | 5·25 | 7·17 | | | |
| | 0·453 | 6·08 | 8·47 | | | |
| | 0·382 | 1·85 | 3·09 | | | |
| | 0·403 | 2·81 | 5·55 | | | |
| 3d | 0·429 | 4·55 | 9·27 | 1·32 | 1·05 | 2·44 |
| | 0·452 | 6·81 | 13·43 | | | |
| | 0·457 | 7·36 | 9·87 | | | |
| | 0·506 | 0·55 | 1·00 | | | |
| | 0·518 | 0·84 | 1·72 | | | |
| 4b | 0·528 | 1·19 | 2·76 | 1·28 | 0·99 | 4·76 |
| | 0.543 | 2·00 | 3·52 | | | |
| | 0·480 | 0·46 | 1·39 | | | |
| 4c | 0·492 | 0·60 | 1·74 | 1·50 | 0·99 | 3·91 |
| | 0·521 | 1·09 | 3·57 | | | |
| | 0·534 | 1·42 | 5·47 | | | |
| | 0·532 | 0·67 | 1·40 | | | |
| | 0·540 | 1·26 | 2·03 | | | |
| 5a | 0·545 | 1·83 | 2·96 | 1·19 | 1·03 | 6·06 |
| | 0·558 | 3·83 | 5·44 | | | |
| | 0·561 | 6·00 | 7·99 | | | |

Although not illustrated in the paper, we also plotted a function of the tensile strength $F\left(\equiv T/\tfrac{1}{2}\frac{s}{v}\frac{\rho}{\rho s}\right)$ as derived by Cheng (1968) versus a function of the packing density, namely $\frac{d}{3}\left(\frac{\rho}{\rho_0}-1\right)$ to obtain values for the quantity $t_o$, which has been defined by Cheng (1968) as the effective range of the attractive forces between neigh-

bouring particles, i.e. their surface separation when the tensile strength is zero. Values of $t_0$ for all the samples are included in Table 1.

*Shear strengths*

The results of the shear tests are summarized in Table 2 and a typical family of yield loci for one of the samples is shown in Fig. 1.

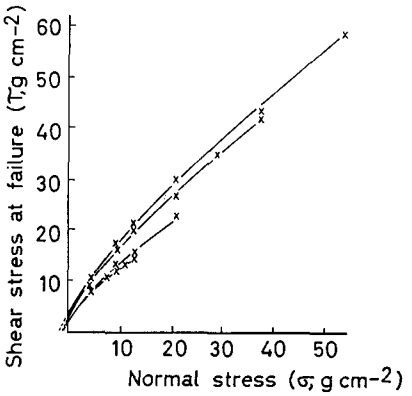


FIG. 1. Yield loci sample 1C.

Analysis of the results shows that all the yield loci conform satisfactorily to the Warren Spring Equation (Ashton & others, 1965)

$$\left(\frac{\tau}{C}\right)^n = \frac{\sigma + T}{T} \qquad (2)$$

so that in every case a graph of log $\tau$ versus log $(\sigma + T)$ gives a good straight line when fitted by regression analysis. An example is given in Fig. 2. From the results, we have obtained values of the cohesion C, the shear index n, the failure factor FF

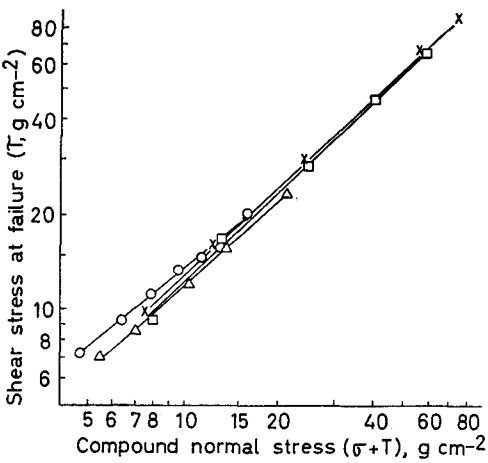


FIG. 2. Log shear stress at failure versus log compound normal stress Sample 1a. ○ Packing density 0·450; △ packing density 0·465; □ packing density 0·484; × packing density 0·485.

(obtained from the unconfined yield stress fc and the major consolidating stress $\sigma_m$) (Jenike, 1961, 1964) and the angle of internal friction $\Delta$ (Williams & Birks, 1967; Kočova & Pilpel, 1972), of the samples, using a computer program (which has been described elsewhere) (Walton, 1973). The values are listed in Table 2.

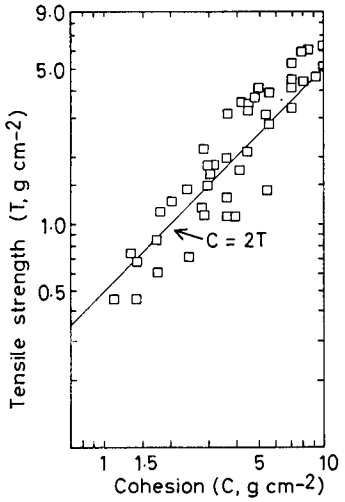


FIG. 3. Tensile strength versus cohesion.

Fig. 3 provides a check on the results and shows that, irrespective of particle size and shape, the relation (Farley & Valentin, 1967)

$$C \approx 2T \qquad (3)$$

is reasonably obeyed over the range of packing densities employed.

## DISCUSSION

To express the effects of particle size and shape on the mechanical properties of the penicillin samples, we have subjected the above experimental results to detailed analysis on a computer (Walton, 1973). The analysis yields relations between the particle size, expressed by V/S, and particle shape, expressed by $\alpha_{s.v.a.}$ of the penicillin samples and their cohesion, tensile strength, shear index, angle of internal friction and failure factor.

The cohesion and tensile strength at all the packing densities investigated are found to be related to the particle size and shape by the expression

$$\log\frac{C}{T} = 1{\cdot}706 - 0{\cdot}213\log(V/S) - 1{\cdot}36\alpha_{s.v.a.} \qquad (4)$$

This is statistically significant at the 5% level and accounts for a substantial part of the variation in the ratio of C/T shown in Fig. 3.

The expression is similar to one derived by Cheng, Farley & Valentin (1968), namely,

$$\log\frac{C}{T} = \frac{1}{6}\log V/S \qquad (5)$$

but contains an explicit term for the effect of particle shape. For example, arbitrarily selecting V/S to be 10$\mu$m, then if the particles have a shape coefficient of 7, the ratio C/T is 2·213, but decreases to 1·360 for those with a shape coefficient of 10.

The corresponding relation for the shear index is found to be

$$(n - 1) = 1{\cdot}329 + 0{\cdot}0083\left(\frac{V}{S}\right) - 0{\cdot}128\alpha_{s.v.a.} \quad .. \quad .. \quad (6)$$

indicating that this parameter is more dependent on the shape of the particles than on their size.

There is still uncertainty in the literature concerning the significance of n, in terms of powder flow (Ashton & others, 1965; Farley & Valentin, 1967; Kočova & Pilpel, 1973), but it now seems that only if the material is behaving as an ideal "simple" powder is n a true measure of the external work being done by the sample when it is sheared (Williams & Birks, 1967).

This work can arise either as a result of dilatancy, which is the expansion of the bed in a direction perpendicular to the direction of shear and which results in a decrease in the packing density, or as a result of realignment or "toppling" of individual particles so that their long axis aligns in the direction of shear.

Both mechanisms can occur simultaneously and it seems logical to suppose that the higher the shape coefficient (i.e. the greater the departure from isometric) the greater will be the tendency for the particles to realign when sheared. Realignment involves less external work than dilatancy and this explains the inverse relation between n and $\alpha_{s.v.a.}$ in equation (6).

The connection between tan $\Delta$ and the particle size and shape is given by

$$\tan\Delta = 0{\cdot}812 + 0{\cdot}0057\,(V/S) + 0{\cdot}0256\,\alpha_{s.v.a.} \quad .. \quad .. \quad (7)$$

This shows again the marked influence of particle shape on the mechanical properties of the penicillin with the angle of friction increasing significantly with increase in shape coefficient. Tan $\Delta$ is a measure of the internal work of friction during shearing and it seems logical that this should increase as the particle shape becomes less regular. However, it is not clear at present why, in the particular case of penicillin, the effect of particle size on tan $\Delta$ should be in the opposite sense and very much smaller than for certain other powders in the same range of sizes (Kočova & Pilpel, 1972) and the point needs to be investigated further.

Turning finally to the failure factor FF, which Jenike (1961, 1964) and others (Williams, Birks & Battacharya, 1971) have suggested is probably the best indicator of how a powder will flow under gravity (in contrast to failing when consolidated and sheared), the relation between FF and the particle size and shape is

$$FF = 6{\cdot}52 + 0{\cdot}434\,(V/S) - 0{\cdot}528\,\alpha_{s.v\,a.} \quad .. \quad .. \quad (8)$$

As expected, this indicates that under gravity the flowability of the penicillin increases with particle size but decreases with increase in shape coefficient.

*Design of equipment*

It seems likely that the flow index which will correlate best with the performance of a powder in filling equipment will depend on the design of the equipment being employed.

Consider that shown schematically in Fig. 4. This is generally suitable for the rapid dispensing of pharmaceutical powders into unit dose containers. The failure properties of the powder under gravity will control its packing density in the hopper and also the rate at which it is withdrawn from it by the auger below.

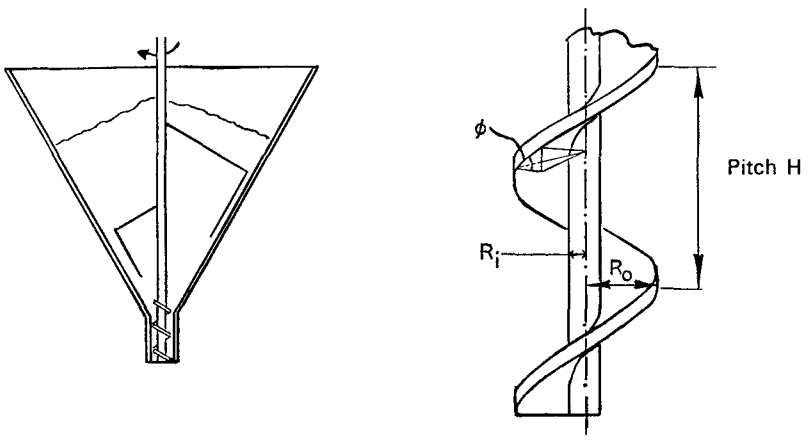


FIG. 4. Hopper and auger feeder.

This auger applies both compressive and shearing stresses to the powder, increasing its packing density. If it is stopped and then started again there will be fluctuations in the amount that it delivers per revolution. The fluctuations, which become increasingly significant as the dose in each container is reduced, arise from fluctuations in the gravity feed and also because of variations in the amounts of powder that break off from the column of material being extruded by the auger. These amounts are likely to be less than anticipated because of the vibrations that occur when the equipment is operating.

The rate at which powder flows from the hopper into the auger will be expected to depend on the value of FF and hence to increase with increase in particle size and to decrease with increase in shape coefficient. But in the auger section, the material is being compressed and it is important that the design should be such that this is minimal, particularly when the material has a high shape coefficient because the tensile strength is then particularly dependent on packing density—see Table 2.

Provided the powder is sufficiently cohesive not to flow when the auger is stopped, the compression on it can be minimized by making the auger as short as possible consistent with the fact that it is being used as a metering device. The spiral, or forcing face of the auger applies stress to the powder at an angle to the horizontal which is defined by its pitch. The area of the face is given by

$$\frac{\pi R_o^2}{\mathrm{Cos}\phi_{R_o}} - \frac{\pi R_i^2}{\mathrm{Cos}\phi_{R_i}} \quad \ldots\ldots\ldots\ldots \quad (9)$$

where $$\phi R_o = \sin^{-1}\frac{H}{2\pi R_o}$$

and $$\phi R_i = \sin^{-1}\frac{H}{2\pi R_i}$$

From this it follows that the angle of the face to the vertical varies along a radius from the axis of rotation, because H is constant, but the radii in the expressions for $\phi$ increase (for example if $R_i = 0{\cdot}282$ cm, $R_o = 0{\cdot}549$ cm and $H = 0{\cdot}635$ cm then $\phi_{R_i} = 21°$ and $\phi_{R_o} = 10{\cdot}6°$). The area of the forcing face per turn of the auger is reduced as H is reduced (for example if $R_i = 0{\cdot}282$ cm and $R_o = 0{\cdot}549$ cm when $H = 0{\cdot}952$ cm the area per turn $= 2{\cdot}55$ cm$^2$; when $H = 0{\cdot}793$ cm, the area per turn $= 2{\cdot}04$ cm$^2$, and when $H = 0{\cdot}635$ cm, the area per turn $= 1{\cdot}53$ cm$^2$).

The fact that the angle of the face to the vertical changes progressively along a radius implies that the resultant of the forces applied to the powder tends to force it from the centre of the auger towards the restraining wall of the pipe in which it is running and to consolidate the powder. This effect can be minimized by designing the auger flight such that, in section, it is not normal to the axis of rotation.

Minimizing the pitch of the auger, H, will ensure that the maximum component of stress is applied vertically: that is, it will tend to move the powder vertically downwards rather than horizontally, but the volume per turn of the auger will thereby be reduced as will be the area of the forcing face. If the auger were to be modified in this way, the throughput would be reduced and the auger would have to turn more to deliver the same dose. But by increasing the value of $R_o$, i.e. using a bigger auger the consolidation could be reduced without any detrimental effect on throughput.

It is now possible to see how changes in the design of the auger might be combined with control over the size and shape of the penicillin particles to achieve maximum uniformity of dose in each container.

If it is assumed that the powder is flowing freely from the hopper into the auger, then any variations in dose will be due solely to variations in consolidation of the powder in the auger section. Let it be assumed that for the particular consolidating stress being applied, the equilibrium packing density has been attained in the auger. Suppose that by modifying the auger, the consolidating stress could be reduced by, say, 30% e.g. from 172 g cm$^{-2}$ to 118 g cm$^{-2}$, this would reduce the tensile strength by between 20 and 50% and would also reduce the variations in the weight of powder being delivered per turn. From Table 1 it is seen that a reduction in tensile strength of 20% could be achieved by increasing the average particle size of the penicillin from 3·9 to 7·2 $\mu$m. Converting this into the corresponding change in the value of FF from equation 8, the same change could also be achieved by reducing the shape coefficient of the particles from 10·06 to 7·60.

Thus for the equipment concerned, it might be found beneficial to make changes in the design of the auger and couple them with closer control of the size and shape of the penicillin particles.

## CONCLUSIONS

The fact that the parameters investigated vary in different ways with the size and shapes of the particles in the various samples of penicillin is presumably because they relate to different mechanical properties of the material.

The cohesion and tensile strength are derived from the portions of the yield loci where one is applying zero or negative normal stresses. The quantity n is a measure of the overall geometrical shape of the loci and depends on the total amount of both internal and external work being done when the powder is sheared under a positive normal stress. Since this work arises from two different causes, namely, dilatancy and realignment of particles, and since the contribution of each alters with the particle

size and shape, it is thought that n taken alone will not be an entirely satisfactory parameter for defining the failure properties of penicillin.

The failure function FF is a useful parameter for describing the flowability of the uncompressed material under the action of gravity and previous workers have shown that there is a direct correlation between the value of FF and a material's flowability.

Tan Δ, on the other hand, is the only parameter of those investigated which relates entirely to the end points of the yield loci, where no external work is being done when the bed of powder is being sheared. It is thus a true measure of the forces of internal friction when the system is in a state of dynamic equilibrium.

The expressions which have been obtained in this work show that the shapes of penicillin particles have at least as much influence as their size on mechanical properties.

Particle shape should therefore be considered when drawing up specifications for handling and processing this, and presumably other materials in pharmaceutical practice.

*Symbols:* C = Cohesion g cm$^{-2}$; $d_a$ = mean particle diameter μm; $F = T/\frac{1}{2}.\frac{S}{V}\frac{\rho}{\rho_s}$; $f_c$ = unconfined yield stress gcm$^{-2}$; FF = failure factor; H = pitch of auger cm; $K_{sa}$ = surface coefficient; $K_{va}$ = volume coefficient; n = shear index; $R_i$ = radius of auger stem cm; $R_o$ = radius of auger face cm; $t_o$ = particle surface separation when T = 0; T = tensile strength g cm$^{-2}$; V/S = particle diameter as ratio of volume/surface area; $\alpha_{s.v.a.}$ = particle shape coefficient; Δ = angle of internal friction; ρ = bulk density g cm$^{-3}$; $\rho_s$ = particle density g cm$^{-3}$; $\rho_o$ = value of $\rho/\rho_s$ when T = 0; φ = angle of auger: σ = Normal stress g cm$^{-2}$; $\sigma_m$ = major consolidating stress g cm$^{-2}$; τ = shear stress g cm$^{-2}$.

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