Table III—Reproducibility of Results

Nadolol	*RSD*, %
Serum, ng/ml	
10	2.22
80	1.00
200	1.41
Urine, μg/ml	
0.04	1.39
20.00	0.73

Standard curves were prepared in the ranges between 0 and 0.03, 0 and 0.2, 0 and 2, and 0 and 20 μg/ml. Fluorescence was proportional to nadolol concentration. Concentrations in all ranges tested produced straight lines that passed through the origin. The fluorescence spectrum of nadolol at different concentrations was recorded (Fig. 3).

The recovery study was carried out by the addition of nadolol in 0.1 *N* HCl to 5-ml serum blanks or 1-ml urine blanks. Recovery from serum varied from 93.3% for a low concentration of nadolol to 103.3% (Table I); from urine, recovery varied from 99.6 to 104% (Table II).

The reproducibility of results was checked by analyzing spiked samples 10 times (Table III).

Standard nadolol acid solutions are stable at room temperature at least 1 week and at 5° at least 3 months.

The method has performed reliably in a number of clinical studies[17]. For example, serum and urine nadolol levels after oral administration of a single 80-mg dose to a male patient are shown in Figs. 4 and 5. It is believed that only unchanged drug produces fluorescence when oxidized and coupled with III. 4-Hydroxynadolol does not fluoresce.

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Influence of Crystal Form on Tensile Strength of Compacts of Pharmaceutical Materials

M. P. SUMMERS *, R. P. ENEVER *x, and J. E. CARLESS

Abstract □ The tensile strengths of compacts of different crystal forms of aspirin, sulfathiazole, and barbital were determined with a modified tablet hardness tester. For each material, the tensile strength could be correlated with the amount of plastic flow and/or crushing undergone by each crystal form during compression.

Keyphrases □ Crystal form—effect on tensile strength of compacts of aspirin, sulfathiazole, and barbital □ Tensile strength—compacts of aspirin, sulfathiazole, and barbital, effect of crystal form □ Aspirin—compacts, effect of crystal form on tensile strength □ Sulfathiazole—compacts, effect of crystal form on tensile strength □ Barbital—compacts, effect of crystal form on tensile strength □ Tablets—aspirin, sulfathiazole, and barbital, effect of crystal form on tensile strength □ Dosage forms—tablets, aspirin, sulfathiazole, and barbital, effect of crystal form on tensile strength

Previously, the use of a physical testing instrument[1] for measurement of the tensile strengths of compacts of pharmaceutical materials was reported (1). A subsequent study (2) indicated that the test could be used to predict the tensile strength of lactose compacts, and another report (3) indicated that this parameter was a fundamental material property independent of the compact dimensions.

The present paper describes the use of a modified tablet hardness tester[2] for measuring the tensile strength of

[1] Instron Engineering Corp., Park Ridge, Ill.

[2] Erweka type TBT tester, Erweka Apparatebau GmbH, Main, West Germany.

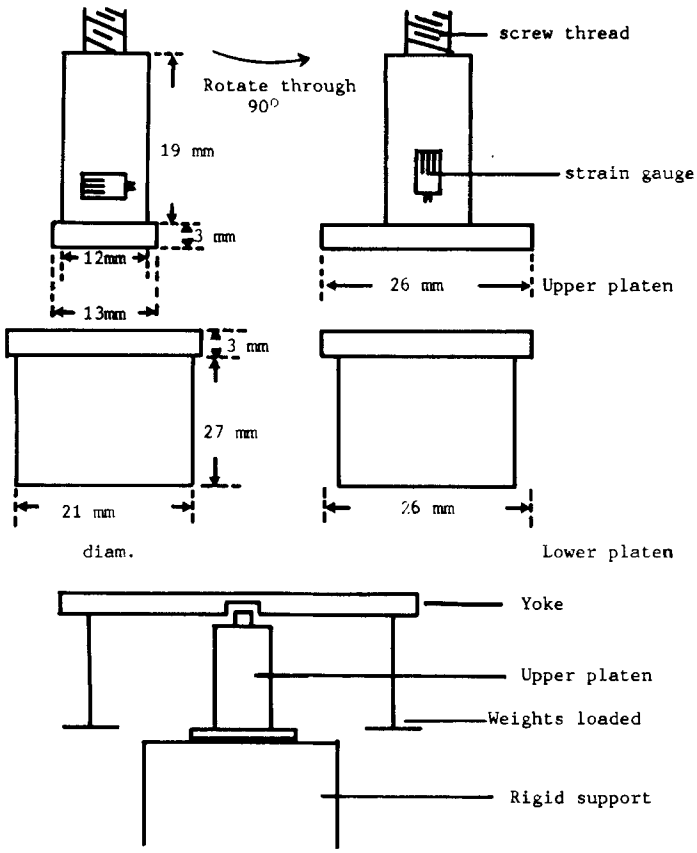

Figure 1—*Diagram of modified platens and calibration of upper platen.*

compacts of various crystal forms of drugs. Such an instrument is of more general use in the pharmaceutical industry than the much more elaborate physical testing instrument. The relationship between the tensile strengths of compacts of different crystal forms of aspirin, sulfathiazole, and barbital and the degree of plastic flow and/or crushing occurring during compact formation also is reported.

EXPERIMENTAL

Modification and Calibration of Tablet Hardness Tester[2]—The platen assembly of the tester (4) was replaced by smooth, flat-faced, platens of 3-mm thick mild steel. The upper platen was 13 × 26 mm, and the lower platen was 26 mm square. To determine the compact breaking load, four foil strain gauges[3] were bonded onto the 12-mm diameter shank of the upper platen (Fig. 1). The gauges were placed diametrically opposite one another in a Poisson arrangement (5) and connected so that each was an active arm of a Wheatstone bridge circuit. They were protected from damage by a coating of a silicone rubber compound[4].

A carrier amplifier[5] (oscillator frequency 5 kHz, input voltage 1 v) was used to energize the bridge network. The output from the network was displayed on a UV galvanometer recorder[6].

The strain-gauge assembly on the upper platen was calibrated by placing a yoke on the shank and loading 1-kg weights onto the yoke to apply compressive forces of up to 12 kg (Fig. 1). The relationship between galvanometer deflection and applied force was recorded and was linear over this range.

Compacts for Tensile Strength Measurements—To evaluate the modified tester, spray-dried lactose[7] (104–152-μm) compacts of 600 and 700 mg were prepared using an instrumented tablet machine[8] to apply axial forces of 1080, 1390, 1720, 2015, 2380, and 3000 kg (6). The compacts were aged for 24 hr before determining their tensile strength. The need to standardize compact age was advised previously (7).

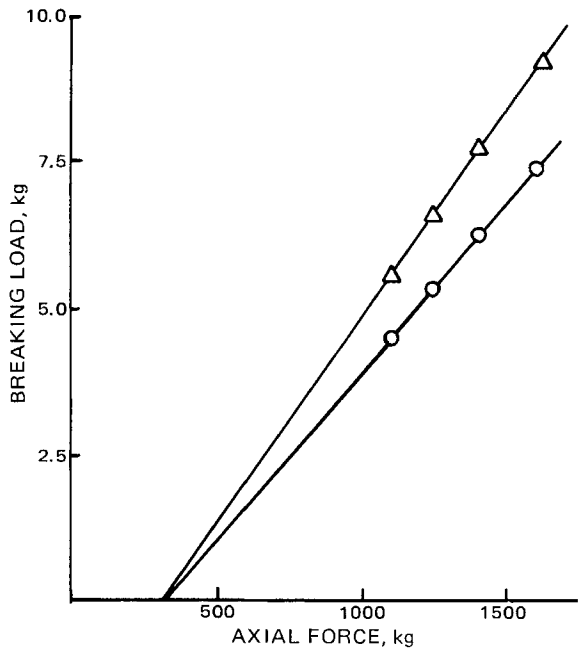

Figure 2—*Breaking load of spray-dried lactose compacts at a range of axial compaction forces. Key: ○, 600-mg compacts; and △, 700-mg compacts.*

Compacts also were produced from various crystal forms of barbital, sulfathiazole, and aspirin. Forms II and III of barbital were obtained by recrystallization of a commercial sample[9] from water and a dilute ammoniacal aqueous solution, respectively; Form I was prepared by heating Form II at 160° until transformation was complete (10–20 min).

Sulfathiazole Forms I and II were produced by recrystallization of sulfathiazole[10] from water and 1-propanol, respectively. Both 190–251- and 104–152-μm fractions of these various crystal forms were used for the compacts. Aspirin Forms I, II, and IV were produced by recrystallization of a commercial sample[11] from 96% ethanol at 20°, *n*-hexane at 0°, and *n*-octane at 20°, respectively. The 250–253-μm sieve fraction was collected in all cases.

With each crystal form, the die of the tablet machine was filled with a weight of material that produced a compact 4.0 ± 0.2 mm in thickness at each force level. These force levels were chosen so that the data could be correlated with the radial stress transmission characteristics of the crystal forms (6). The compacts also were stored for 24 hr before testing.

To characterize the various crystal forms and to ensure that transformation did not occur during the compaction process, crystals and compacts were subjected to differential scanning calorimetry[12] and, where appropriate, IR spectrophotometry[13] as described elsewhere (6).

Measurement of Tensile Strength—The dimensions of each compact were measured with vernier calipers (±0.01 mm) prior to the test. Strips of paper (1.3 mm wide × 0.1 mm thick) were placed between the platens and the compact as padding material throughout the test. The machine was operated in the normal manner to apply an increasing force to the compact *via* the top platen at a rate of 0.4 kg/sec.

When the compact failed, the tester stopped automatically and the galvanometer deflection of the UV recorder rapidly returned to zero. The failure load was calculated from the maximum galvanometer deflection. Only data for those compacts that appeared to have failed in tension were

[3] Micro Measurements type EA-06-125-BT-120, 120 ± 0.15% Ω resistance, Welwyn Strain Measurements Ltd., Basingstoke, England.
[4] R.S. Components, London, England.
[5] Honeywell type 2506 carrier amplifier, Honeywell Controls Ltd., Hemel Hempstead, England.
[6] Honeywell 1706 Visicorder equipped with type BB250A mirror galvanometer, Honeywell Controls Ltd., Hemel Hempstead, England.
[7] α-Monohydrate form, McKesson and Robbins Ltd., Kent, England.
[8] Manesty E2 tablet machine, Manesty, Speke, Liverpool, England.
[9] British Drug Houses Ltd., Poole, Dorset, England.
[10] Evans Medical Ltd., Liverpool, England.
[11] Aspro-Nicholas Ltd., London, England.
[12] DSC 1, Perkin-Elmer, Beaconsfield, Bucks., England.
[13] Unicam SP200 recording spectrophotometer, Pye-Unicam, Cambridge, England.

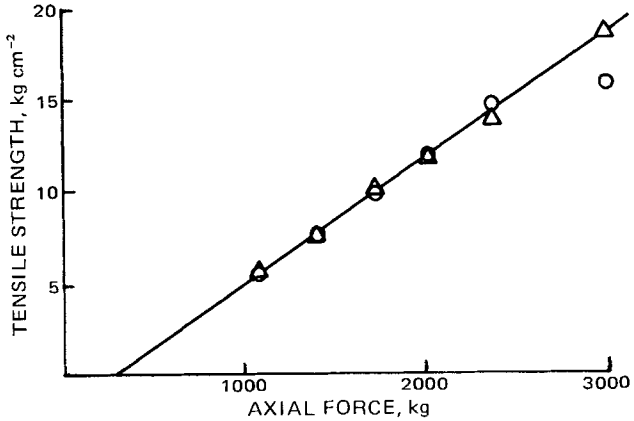

Figure 3—*Variation of tensile strength of lactose compacts with applied axial force. Key: O, 600-mg compacts; and Δ, 700-mg compacts.*

used. Tensile failure was checked by visual observation of the fractured compacts. The tensile strength, σ, of each compact was calculated using:

$$\sigma = \frac{2P}{\pi Dt} \qquad \text{(Eq. 1)}$$

where P is the breaking load, D is the compact diameter, and t is the compact thickness. An average value was determined from the failure of five compacts prepared at each compression level.

RESULTS AND DISCUSSION

Evaluation of Tensile Tester Using Lactose Compacts—Figure 2 shows the relationship between breaking load, P, and the axial force of compaction for 600- and 700-mg lactose compacts; differing linear relationships were obtained. If, however, the data are plotted as tensile strength against axial force (Fig. 3), then all points fall on a single straight line. Repeated determinations gave results that fell on this line. If only the compacts failing in tension are used to calculate results, the reproducibility of the measurements is good and the modified tester affords a method of tensile strength measurement. Furthermore, since tensile strength is independent of compact dimensions, it is a fundamental material property.

The rejection rate of compacts not showing tensile failure varied considerably. At the lowest compression forces used, and with materials prone to lamination and capping, the rejection rate was 50–60%. For materials possessing good bonding characteristics, the rejection rate could be as low as 5%. This variability in rejection rate may be due to the fact that the loading rate of 0.4 kg/sec may be excessive and not ensure uniform stress distribution in the compact on each occasion. This problem is aggravated by unequal distribution of density (8) and hardness (9) in the compact. Another factor is that, at the low compression forces where there may be little appreciable bonding between the particles, the elastic rebound of the unbonded particles may adversely affect the stress distribution throughout the compact because of flaw formation.

Figure 3 also shows that deviation of mean tensile strength from the linear relation occurred with the 600-mg compacts at the highest compression force used. The relatively low value of tensile strength under these conditions is attributed to the fact that no significant additional particle–particle bonds are formed at these higher pressures and the tensile strength tends to a constant value. Rees and Shotton (10) noticed a similar effect when investigating the effect of compact dimensions on the crushing strength of sodium chloride tablets.

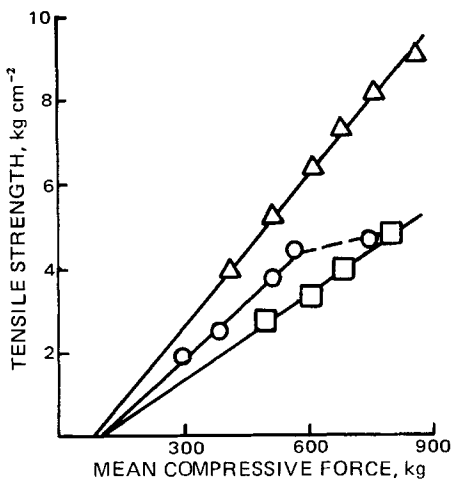

Figure 5—*Tensile strength of compacts of barbital polymorphic forms (104–152 μm). Key: O, Form I; □, Form II; and Δ, Form III.*

Influence of Crystal Form on Tensile Strength of Pharmaceutical Compacts—The relationships between tensile strength and mean compression force (mean of axial and radially transmitted forces) for the various crystal forms of sulfathiazole, barbital (104–152 μm), and aspirin (253–353-μm size) are shown in Figs. 4, 5, and 6, respectively. For any given mean compressive force, the tensile strength of sulfathiazole compacts was Form II > Form I (Fig. 4); for barbital, it was Form III > Form I > Form II (Fig. 5).

The tensile strength of a compact of any material is a function of the area of contact between the particles and the strength of the bond produced between them. Since the less stable polymorphic form of a material is considered to possess higher potential energy and weaker bonding (11), the strength of the particle–particle bond should be less than that of the stable form. However, the area of contact between particles depends on the degree of plastic flow or crushing of particles during compression, and this is likely to be greater for an unstable polymorphic form that will have lower resistance to plastic flow and crushing.

The degree of plastic flow and/or crushing during compression was evaluated by Leigh (12), who measured the change in the relative density of a compact, ϕ, during this stage of compaction. Summers (13) determined the ϕ values for the various crystal forms of sulfathiazole and barbital (104–152 μm) used in this study. These data are shown in Table I together with the tensile strength value of the compacts at an arbitrary mean compression force of 400 kg; a correlation between ϕ and tensile strength existed. Since barbital Form II and sulfathiazole Form I are the stable polymorphic forms of the two materials and compacts of these forms have the lower tensile strengths, the findings suggest that the overriding influence on compact strength is the area of contact developed

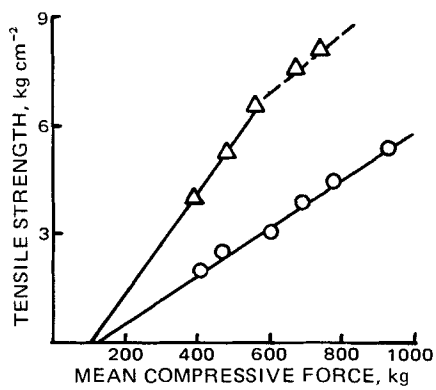

Figure 4—*Tensile strength of compacts of sulfathiazole polymorphic forms (104–152 μm). Key: O, Form I; and Δ, Form II.*

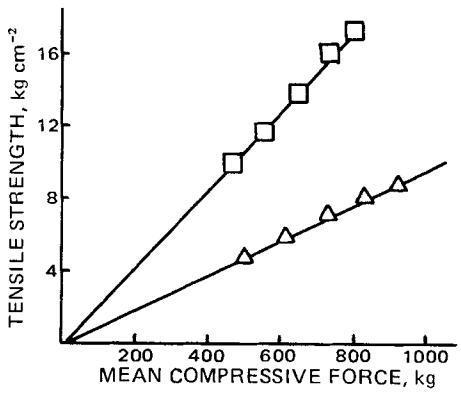

Figure 6—*Tensile strength of compacts of aspirin crystal forms (250–353 μm). Key: Δ, Form I; and □, Form IV.*

Table I—Comparison of Tensile Strength of Compacts Compressed at a Mean Force of 400 kg and the Relative Density Change Occurring during Plastic Flow and/or Crushing, ϕ

Crystal Form	Tensile Strength, kg/cm^2	ϕ
Barbital (104–152 μm)		
Form I	2.8 ± 0.1	0.21 ± 0.008
Form II	2.0 ± 0.2	0.21 ± 0.008
Form III	3.8 ± 0.1	0.23 ± 0.007
Sulfathiazole (104–152 μm)		
Form I	1.9 ± 0.1	0.22 ± 0.008
Form II	4.2 ± 0.2	0.24 ± 0.008
Aspirin (250–353 μm)		
Form I	3.8 ± 0.1	0.14 ± 0.008
Form IV	8.4 ± 0.2	0.23 ± 0.007

between particles in the powder bed rather than the bond strength between particles. Support for this hypothesis is obtained from the data relating particle size to tensile strength of barbital Form II and sulfathiazole Form I compacts (Table II). At any mean compression force, the smaller particle-size fraction of both drugs produced the stronger compact. There will be a greater number of point contacts within compacts made from the smaller fraction and, hence, a greater area of contact between particles.

Compacts of the aspirin crystal forms also showed differences in tensile strength at a given mean compression force (Fig. 6). Tensile strength values could not be obtained for compacts of aspirin Form II because of the layering tendency of the needle-shaped crystals (6). When Form II compacts were subjected to diametral crushing, the compacts laminated.

Table II—Influence of Particle Size on the Tensile Strength of Barbital and Sulfathiazole Compacts over a Range of Mean Compression Forces

Mean Compressive Force, kg	Tensile Strength, kg/cm^2 ± 0.1			
	Barbital Form II		Sulfathiazole Form I	
	104–152 μm	190–251 μm	104–152 μm	190–251 μm
610	3.4	2.9	3.3	2.5
713	4.1	3.3	4.0	2.7
815	4.8	3.7	4.7	2.9
917	5.5	4.3	5.3	3.1

As with the polymorphic forms of sulfathiazole and barbital, there was a correlation between ϕ and the tensile strength of the compacts for aspirin Forms I and IV. The lower melting-point Form IV had the higher tensile strength at any given mean compression force, again indicating that the area of contact between particles is the overriding influence on compact strength for materials existing in different crystal forms.

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Degradation Kinetics of a Substituted Carbinolamine in Aqueous Media

H. V. MAULDING ˣ and M. A. ZOGLIO *

Abstract □ The apparent first-order breakdown of the medicinally active agent 3-(*p*-chlorophenyl)-2-ethyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-ol was studied in aqueous solutions where dehydration gave the unsaturated compound 3-(*p*-chlorophenyl)-5,6-dihydro-2-ethylimidazo[2,1-*b*]thiazole. This thiazole was the primary solvolytic product produced in approximately quantitative yields for the temperature range studied and ostensibly underwent no further reaction in acidic media even on prolonged heating. Investigations were carried out at various pH values in standard buffers at constant ionic strength. The ionization constants of the compounds are reported as well as the apparent activation energies for the degradation in acid and acetate buffers. The influence of ionic strength on the velocity constant was determined.

Keyphrases □ Thiazol-3-ol, substituted—kinetics of degradation in aqueous media, effect of temperature, pH, and ionic strength □ Degradation kinetics—substituted thiazol-3-ol, in aqueous media, effect of temperature, pH, and ionic strength □ Kinetics, degradation—substituted thiazol-3-ol, in aqueous media, effect of temperature, pH, and ionic strength □ Anorexic agents, potential—3-(*p*-chlorophenyl)-2-ethyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-ol, kinetics of degradation in aqueous media, effect of temperature, pH, and ionic strength

The degradation kinetics of 3-(*p*-chlorophenyl)-2-ethyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-ol[1] (I) were investigated in aqueous solution at varying hydrogen-ion concentrations.

Compound I exhibits anorexic activity, and its breakdown in aqueous media is important in the formulation of

[1] No. 43976, Sandoz Pharmaceuticals, Hanover, NJ 07936.