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A comparative evaluation of the mechanical strength of sealed and unsealed hard gelatin capsules

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Summary

The purposes of banding and sealing of hard gelatin capsules are well known; however, the effects of these processes on shell fragility have not been documented. In this study the effect of banding and fluid sealing (both water and a 50:50 water/ethanol mixture) on shell mechanical strength was evaluated using a modified capsule plug hardness tester. Banded capsules were prepared using an Elanco laboratory model banding machine. Fluid sealed capsules were prepared by a manual sealing process. Failure force data were collected for natural and white opaque size 0 Elanco capsules and natural size 0 Capsugel capsules. Fluid sealed capsules were found to fail at lower applied crushing forces than banded capsules. The effect of banding on shell fragility was found to be slight and the forces of failure were comparable to those of unsealed capsules. In some cases, visual observations of fragility during the crushing event correlate well with low failure forces. Work of failure was also assessed and found less discriminating than the force of failure.

Introduction

The unfortunate earlier incidents of capsule tampering have in recent years sparked a considerable interest in methods of sealing hard gelatin capsules as a means of making capsules tamper resistant and tamper evident. Other reasons for sealing hard gelatin capsules include the containment of liquids and semisolids and the enhancement of the stability of capsule contents by providing an effective barrier to atmospheric oxygen (Jones, 1987; Shah and Augsburger, 1989).

The most common method of sealing hard gelatin capsules is banding which involves the application of a wet band of gelatin around a capsule to seal the two halves together. Modern, high speed banding equipment has been described (Jones, 1987). Hard gelatin capsules also may be sealed by a fluid process wherein the cap and body portions are fused together where they overlap by wetting the interface with a hydroalcoholic solution and subsequent drying at moderate temperatures (Wittwer, 1985).

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The hard gelatin capsule requires sufficient mechanical strength to withstand the forces it experiences during bulk handling, packaging, and subsequent usage, such as removal from a blister. These forces are applied mainly to the side walls of the capsule. The strength of the film is a function of the nature and type of gelatin used, the gelling and drying processes, and the amount of moisture remaining in the gelatin film. The empty capsule contains between 13 and 16% moisture which functions as a plasticizer for the film. If the moisture content falls below a critical value, the film becomes brittle. Few studies have appeared in the literature dealing with the important issue of mechanical strength of the gelatin capsule and the effect of such variables as moisture content and storage conditions, and no studies have addressed the effect of various banding and sealing processes. Kontny and Mulski (1989) utilized a previously developed sorption-desorption moisture transfer model to predict the equilibrium relative humidity in a system of filled gelatin capsules. They related this relative humidity to capsule brittleness and found that brittleness becomes prevalent at relative humidities (RH) below about 40%. More recently, Liebowitz et al. (1990) reported increased brittleness when hard gelatin capsules were exposed to elevated temperatures or reduced humidity. Increased brittleness was correlated with glass transition temperature (t_g) for capsules stored at elevated temperatures. Capsules stored 24 h at 35°C exhibited a higher t_g than those stored 24 h at 21°C, indicating increased brittleness and reduced plasticity. No t_g was observed for capsules stored 24 h at 75°C.

The present study addresses the effects of fluid sealing and banding on gelatin capsule mechanical properties, with the aim of determining the following: To what extent do these sealing processes affect the mechanical strength of the shell wall? Does the entrapped air inside the sealed capsule influence the apparent resistance of the wall to deformation and/or shattering? Are the results of a brittleness study of empty capsules applicable to filled capsules? How is shell mechanical strength affected by the presence of an opacifying agent?

Materials and Methods

Size 0 natural and white opaque Posilok® (Elanco Qualicaps, div. Eli Lilly and Co., Indianapolis, IN) and natural Conisnap® (Capsugel, div. Warner-Lambert Co., Greenwood, SC) capsules were studied. Empty capsules were used in all cases except those which were plug filled for the purpose of studying the effect of plug fill on the force of failure. Plug filled capsules contained a placebo formulation consisting of anhydrous lactose, NF ('direct tableting' grade, Sheffield Products, Norwich, NY) and magnesium stearate, NF (Mallinckrodt Inc., St. Louis, MO). Capsules used in sealing experiments were conditioned at 40% RH and 25°C for 1 week before being subjected to compression failure tests. Capsule samples stored for 2 weeks under these conditions were found to have comparable moisture content, ensuring that moisture equilibrium was achieved in 1 week. After conditioning, all capsules were found to have a moisture content within a narrow range of 13.4–14.4% by use of a moisture analyzer (Computrac®, model MAX-50, C.T. Instruments, Inc., Tempe, AZ) at a temperature of 145°C. Capsules used in moisture studies were conditioned for 1 week at various humidities and 25°C. Moisture content was assessed using the same method. Reported values are means of three determinations.

Banding

Banded capsules were prepared using a bench top Elanco Quali-seal® banding machine and the supplied standard gelatin banding kit. Banded shells were allowed to dry on paper lined trays and then conditioned.

Fluid sealing

Fluid sealed capsules were prepared by wetting the outer, open end portion of the capsule body by rotating the outer body surface against a mass of laboratory tissue saturated with the sealing fluid. The wetted outer body was then placed into the cap and twisted to distribute the fluid. The capsules were allowed to dry on paper lined trays and then conditioned. The two fluids used were purified water and a 50:50 (w/w) mixture of alcohol and purified water.

Measurement of force of failure

A previously described capsule plug hardness tester was used to determine the mechanical strength of the capsule shells (Shah et al., 1986). A vertically mounted motor-driven mechanical slide assembly (Unislide model B4009P20J, Velmex Inc., Bloomfield, NY) was fitted with a 2 mm diameter flat faced cylindrical probe and a piezoelectric load cell (Kistler model 9712A5, Kistler Instruments Inc., Amherst, NY). During operation, the probe is driven (1.1 mm/s) against the side wall of the capsule where the cap overlaps the body. This site was selected because it is along the side wall where the capsule mainly experiences stress during bulk handling, packaging, removal from a blister, etc. The signal from the load cell was amplified and voltage was then measured on a strip chart recorder. The peak force was taken as the force of failure. All values reported are means of 25 determinations. Also, based on visual observation the capsule shells were classified into one of two categories. The first category consisted of those capsules exhibiting glass-like shattering or 'easy failure.' Those exhibiting a more plasto-elastic deformation (flexing) did not fail easily and were placed in the second category. An apparent critical value of 2 kg crushing force was observed which separates the capsules into the two categories (see Figs 1, 3 and 5). This figure is only an apparent, observed value and has no statistical origin.

This procedure differs from that reported by Kontny and Mulski (1989) who did not actually measure failure force. They applied a uniform force in crushing individual capsules with the bottom of a beaker and reported the percentage of capsules exhibiting brittleness. The present procedure is similar to that employed by Liebowitz et al. (1990) except that the latter group applied force to capsules via a 1.5 inch diameter circular platen.

Moisture studies

Posilok® natural unsealed capsules were equilibrated within the range of relative humidities from 10 to 90% in desiccators before testing as described above. Moisture content and force of failure measurements were subsequently obtained.

Measurement of work of failure

Work of failure measurements were performed on sealed and unsealed natural Posilok® capsules. Since the head travel speed of the test probe is constant, the displacement of the platen is directly proportional to time. The area under the force-time profile was measured using a planimeter and was converted to work of failure (J). All values reported are the means of 10 determinations.

Data analysis

In each group of prepared capsules a Tukey's multiple comparison test was made with all pairwise comparisons between the mean forces of failure of unbanded, banded, water sealed and water/ethanol sealed capsules. All groups of prepared capsules, i.e., (i) empty white opaque Posilok®, (ii) filled natural Posilok® and (iii) empty natural Conisnap®, were tested against a group of empty natural Posilok® capsules. An *F* test was used to show effects of: (1) the presence of an opacifying agent, (2) the presence of a plug fill and (3) capsule brand on the mean force of failure. This test was carried out for all treatments: (a) unbanded, (b) banded, (c) water sealed and (d) water/ethanol sealed. Assumptions of data normality and homogeneity were tested and were found to be valid. The statistical software package X-Stat (John Wiley & Sons, Inc.) was used to perform one-way ANOVA on the data. Other calculations for *F* tests and Tukey's tests were performed manually.

Results and Discussion

Effect of entrapped air

Initial experiments were performed on sealed and unsealed natural Elanco Posilok® capsules with and without the presence of a hole. For this study, a single 1 mm diameter hole was bored into the body end of test capsules with a manually

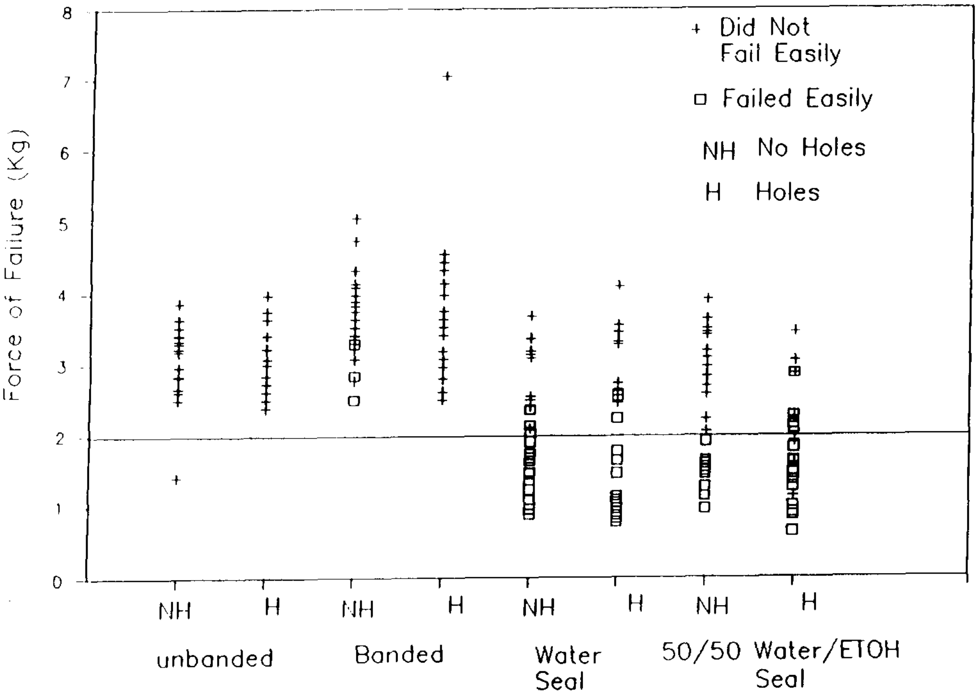

Fig. 1. Effect of entrapped air on capsule mechanical strength.

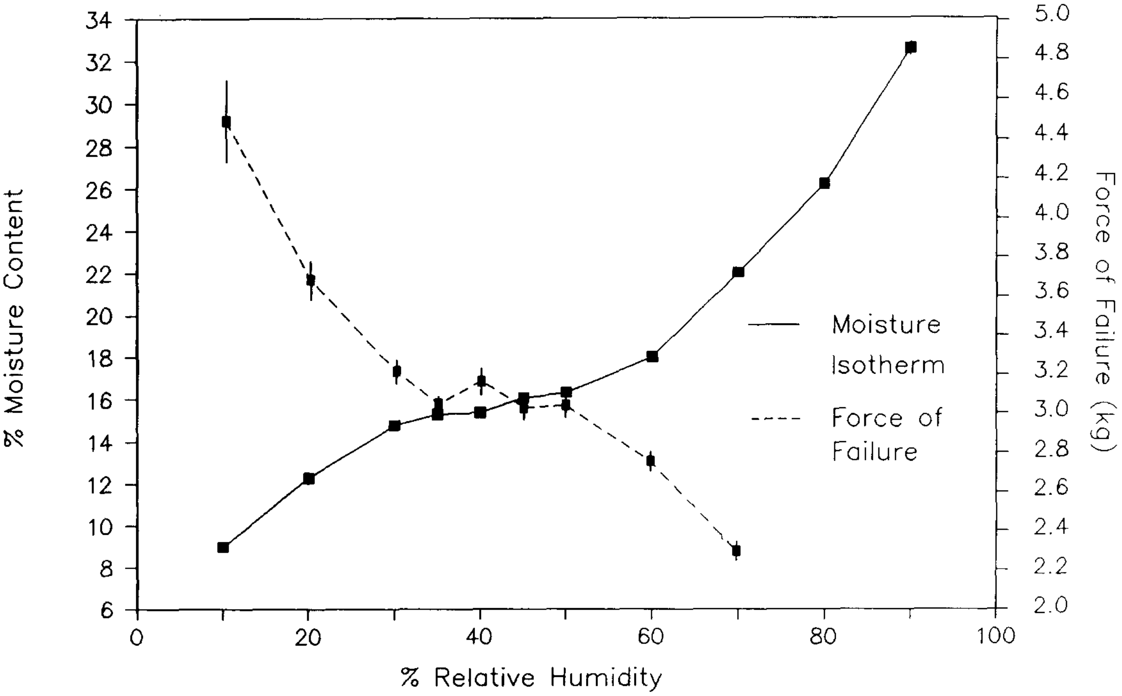

Fig. 2. Effect of humidity on shell mechanical strength and equilibrium moisture content at 25°C.

operated drill. Entrapped air was suspected to cause data bias, especially in the band-sealed case, by providing a uniform resistive force inside the sealed capsule; however, no noticeable differences were seen when force of failure was assessed (Fig. 1). In these preliminary experiments no statistical tests were performed. Capsules used in further experiments did not possess holes.

Effect of humidity

At high humidities, shells become soft and tacky and storage below the optimum humidity range results in brittle shells. Trends of this nature are also evident in the force of failure of hard gelatin shells stored at various humidities. As can be seen in Fig. 2, lower forces of failure are observed for capsules which have been stored in high humidity conditions. These capsules, having higher moisture content are more plasto-elastic in nature and can relieve applied stress easily. Those capsules stored at extremely high humidity became so easily deformable that a determination of breaking force was impossible. Furthermore, complete fusion of the cap and body occurred creating a soft, flexible balloon-like shell. Capsules stored in low humidity conditions are brittle due to lower moisture content and can not easily relieve applied stress. Therefore, the shell resists deformation and a higher stress is developed before failure occurs. During the crushing event these shells visually shatter like glass. In addition to these extremes at low and high humidity, an apparent plateau exists in the force of failure profile in the same range of relative humidities where little change occurs in moisture content. Gelatin shells typically exhibit sigmoidal moisture sorption isotherms resembling type 2 isotherms (Lowell and Shields, 1984) having plateau-like regions or regions of relatively small change in moisture content at these relative humidities (Ridgeway, 1987).

The behavior of capsules when exposed to a full range of humidities offers evidence of the direct role of moisture in the mechanical strength of hard gelatin capsules. When humidity and moisture content are controlled, as in the subsequent experiments, any differences in the force required to break shells are attributable only to factors related to the nature of the joining of the cap and body. However, under these conditions, the relationship between the failure force and the type of failure (plasto-elastic vs brittle behavior) was found to be reversed.

Within group comparisons

All groups of empty shells examined showed statistical differences between mean forces of failure for all pairwise comparisons made within a capsule group except for one (Table 1). Natural Posilok® capsules showed no difference in failure force between those made by water sealing and water/ethanol sealing. Plug filled capsules required relatively high breaking forces and showed mixed effects when all pairwise comparisons were

TABLE 1

Results of Tukey's multiple comparisons test at the 5% level for each treatment

Capsule group	Contrast					
	U vs B	U vs W	U vs WE	B vs W	B vs WE	W vs WE
Elanco Natural	S	S	S	S	S	NS
Elanco White Opaque	S	S	S	S	S	S
Elanco Natural Filled	S	NS	NS	S	S	NS
Capsugel Natural	S	S	S	S	S	S

Capsule groups: U, unsealed; B, banded; W, water fluid sealed; WE, water/ethanol fluid sealed. S, significant differences between mean forces of failure; NS, no significant difference between mean forces of failure.

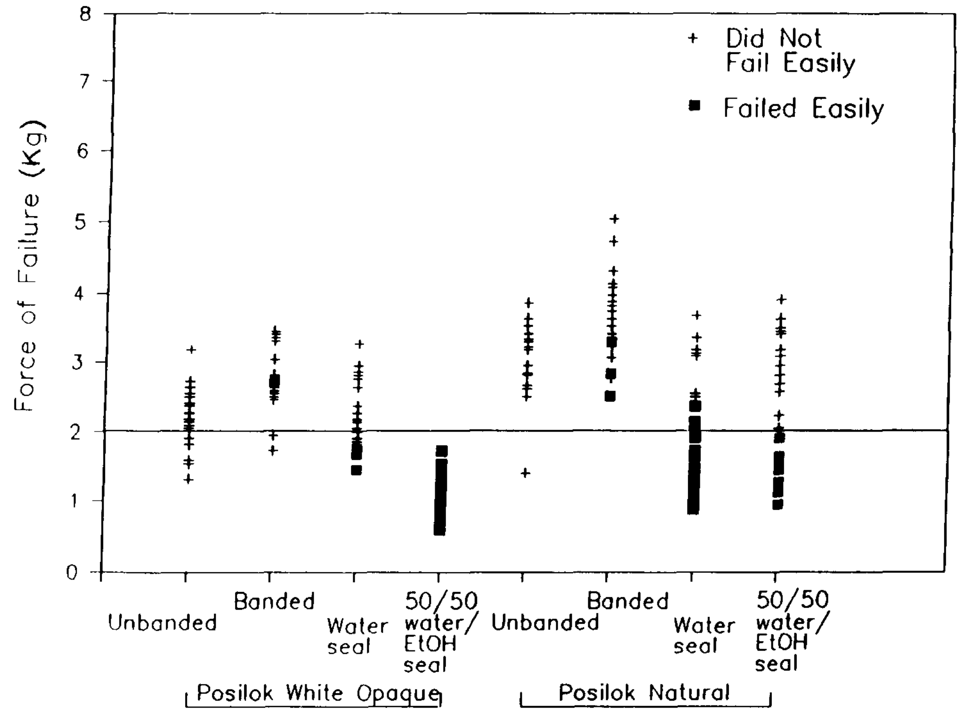

Fig. 3. Effect of an opacifying agent on capsule mechanical strength.

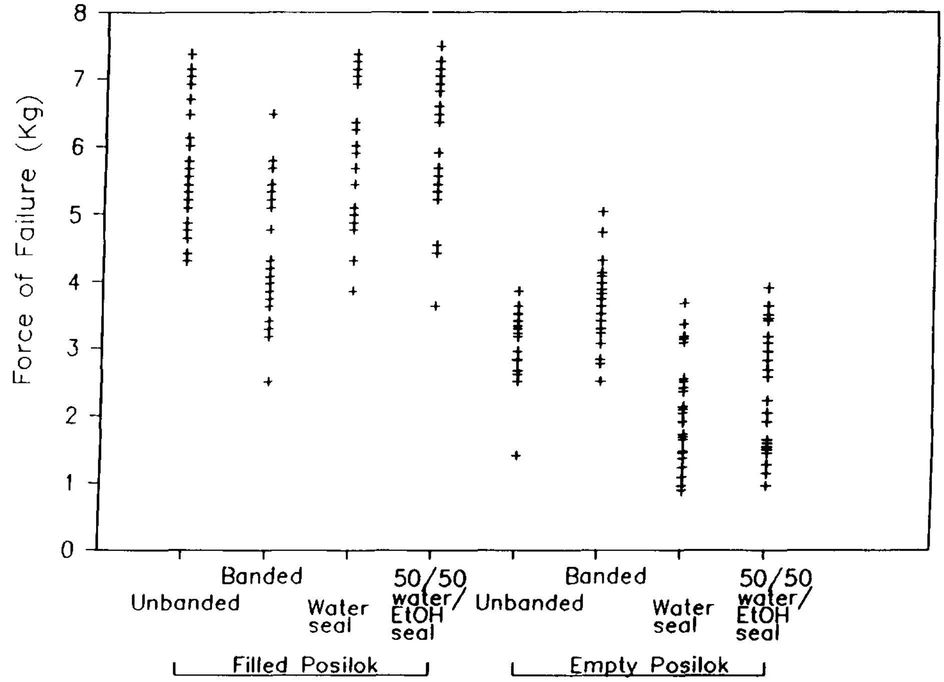

Fig. 4. Effect of plug fill presence on capsule mechanical strength.

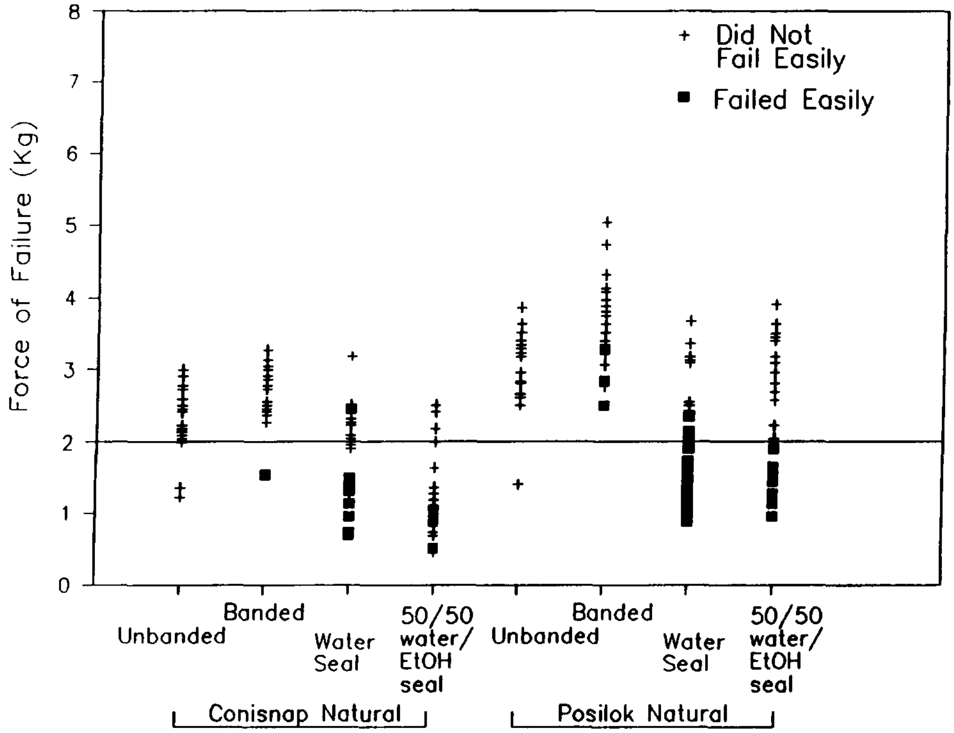

Fig. 5. Effect of brand on capsule mechanical strength.

made within this group. Shell strength alone is not the only parameter being measured here as explained below.

If the data from plug filled capsules are ignored because the presence of plug fill does not allow the assessment of true shell fragility, then in only one case (water vs water/ethanol sealing in natural Posilok® capsules) is there no significant difference between treatments in a group of capsules. This occurrence undoubtedly indicates

TABLE 2

Results of F-tests for between group comparisons of capsule groups when tested against empty natural Elanco Posilok® capsules

Capsule group	Treatment			
	Unbanded	Banded	Water sealed	Water/ethanol sealed
Elanco White Opaque	$p < 0.005$	$p < 0.005$	NS	$p < 0.005$
Elanco Natural Filled	$p < 0.005$	$p < 0.005$	$p < 0.005$	$p < 0.005$
Capsugel Natural	$p < 0.005$	$p < 0.005$	$0.05 < p < 0.1$	$p < 0.005$

NS, no significant difference between mean forces of failure.

that the various sealing processes do have a dramatic effect on the mechanical nature of hard gelatin capsules.

Between group comparisons

The results for the between group comparisons can be seen in Figs 3–5 and Table 2. Opaque capsules, when tested against natural capsules, showed an overall decrease in force of failure for all treatments except water sealing. The opacifying agent may interrupt the gelatin network and decrease the overall strength of the gelatin film (Fig. 3). Plug filled capsules again showed mixed effects as above. The force measured here is much greater than that of empty shells and is really a combination of shell breaking and plug deformation. The presence of a plug hinders the assessment of inherent shell fragility and offers no protection to the shell when forces are applied. Compared to Posilok® capsules, Conisnap® capsules showed a lower force of failure in all cases, both unsealed and sealed (Fig. 5).

TABLE 3

Means and standard deviations of work of failure for natural Elanco Posilok® capsules

Work of failure (J)	Treatment			
	Unsealed	Banded	Water sealed	Water/ ethanol sealed
Mean (SD)	0.0788 0.0308	0.0795 0.0107	0.0107 0.0201	0.0201 0.0103

Differences between brands may be attributable to differences in the character of the gelatin used, shell formulation, the manufacturing procedure, and shell history such as aging and storage conditions.

Work of failure

Work calculations previously have been used to advantage in the study of tablet compaction

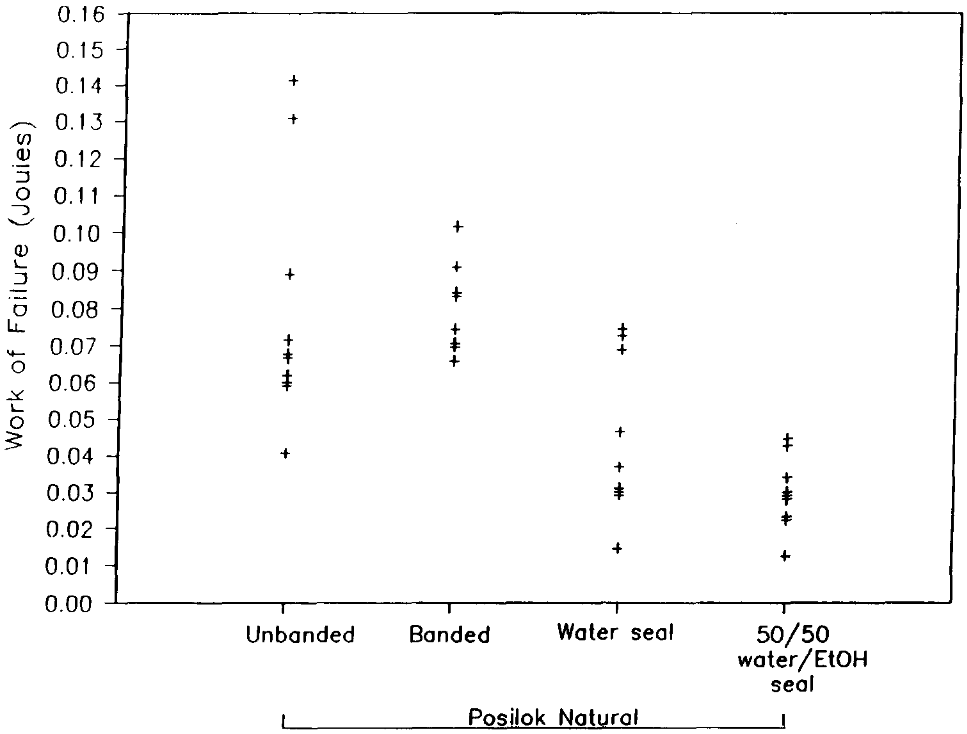

Fig. 6. Work of failure as a measure of capsule shell mechanical strength.

TABLE 4

Results of Tukey's multiple comparisons test at the 5% level (force vs work)

Fragility parameter	Contrast					
	U vs B	U vs W	U vs WE	B vs W	B vs WE	W vs WE
Force	S	S	S	S	S	S
Work	NS	S	S	S	S	NS

U, unsealed; B, banded; W, water fluid sealed; WE, water/ethanol fluid sealed; S, significant difference between mean forces of failure; NS, no significant difference between mean forces of failure.

(Celik and Marshall, 1989) and in assessing the mechanical strength of compressed tablets (Patel and Staniforth, 1987). Based on such studies, work of failure (Table 3) was thought to provide a better measure of the mechanical strength of shells than failure force alone because work calculations incorporate more information. Unlike the failure force, which is a single, peak value, the work of failure is the integration of the applied force over the distance travelled by the probe. When force and work are tested statistically, making all pairwise comparisons between methods of sealing, work does not discern differences as well as force (Fig. 6 and Table 4). Thus, in the present study, work of failure did not appear to offer any advantages over the more simply measured failure force in characterizing shell strength. However, further studies employing force-displacement information may provide additional useful information on shell deformation characteristics.

Conclusions

Differences in mechanical strength between capsules sealed by different methods may be due to the nature of fusion of the cap and body. With fluid sealing, dissolution of gelatin occurs between the cap and body. After drying, bridges of gelatin remain which serve to hold the cap and body together. The relatively large area over which this joining occurs may be responsible for the lower stresses required for splitting of the shell. When flexed, the cap and body cannot move independently during the crushing event to relieve stress, and thus these fluid sealed capsules tend to fail in a more brittle fashion than do banded capsules. Banded capsules possess a gelatin band around the outer junction of the cap and body which may not hinder the independent movement of the cap and body to the same degree as fluid sealing. Greater forces may be sustained and failure tends to be more plasto-elastic in nature.

In general, fluid sealing decreases mechanical strength and banding increases the strength of hard gelatin capsules. The reduction in strength due to fluid sealing may be further enhanced when water/ethanol mixtures are used as sealing fluids as compared to water sealing alone. The presence of plug fill does not allow detection of inherent shell fragility and does not protect the shell during load application. Sealed shells maintain their deformation character (plasto-elastic or brittle) even in the presence of plug fill. The opacifying agent decreases shell mechanical strength in unsealed and sealed capsules, most likely due to interruption of the gelatin network. Work of failure did not prove to be a better measure of shell fragility than force of failure; however, further evaluation of this parameter is needed.

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