DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(6), 995-1010 (1990)

DETERMINATION OF HARD GELATIN CAPSULE BRITTLENESS USING A MOTORIZED COMPRESSION TEST STAND

S. M. Liebowitz*, W. A. Vadino and T. J. Ambrosio

Schering-Plough Research
2000 Galloping Hill Road
Kenilworth, NJ 07033

ABSTRACT

Hard gelatin capsules are solid dosage forms containing powders, granulations, or pellets enclosed in a hard soluble shell. Recent guidelines for submitting documentation for the stability of human drugs and biologics to the FDA have requested test data for capsule brittleness. A simple test has been developed using a compression gauge to quantify the force required to fracture and/or shatter hard gelatin capsules. The data generated from this test can be utilized for dosage form stability assessment as well as quality control and quality assurance of capsules prior to their use in dosage from manufacture.

INTRODUCTION

Hard capsules are solid dosage forms containing medicament(s), with or without diluents enclosed in a hard

* To whom inquiries should be addressed.

TABLE 1

HARD GELATIN CAPSULE DEFECTS

Nonuniformity of shape
Nonuniformity of size
Surface spots
Dents
Mottling or non-uniformity of color
Thin or "weak point" area
Nonsmooth surface
Surface breaks or fractures

soluble shell prepared from a gelatin base containing glycerin or other suitable plasticizers. The hard capsule itself consists of two pieces, i.e. the base and the cap, and may also contain an additional gelatin sealing band to prevent tampering.

General manufacturing specifications for hard gelatin capsules as described by capsule shell manufacturers include dimensional specifications, i.e. weight, size, shape, wall thickness, moisture content, and physical appearance characteristics[1,2]. Table I lists common physical defects of capsule shells. Capsule product stability profiles evaluate for capsule color, physical appearance, shape, dissolution, assay and moisture of contents. Recently, guidelines for new drug applications (NDA) have recommended

obtaining data on capsule brittleness[3]. While capsule manufactures may routinely evaluate capsules for brittleness, this is not necessarily true of the end user.

In this study we report a simple test to quantify capsule brittleness as a function of applied compression force. Capsules have been stored at various constant relative humidity conditions and evaluated for brittleness as a function of applied compression force.

EXPERIMENTAL

Materials

Maroon size "0" ADE and EBW capsules, (Elanco Qualicaps) were selected for this investigation.

Constant humidity solutions were prepared with reagent grade salts (Aldrich Chemical).

Relative Humidity Determinations

Saturated aqueous solutions of lithium carbonate, potassium acetate, calcium chloride, and potassium carbonate containing an excess amount of solute were maintained in enclosed desiccator chambers at 22° ± 0.5°C. A desiccator containing calcium sulfate (Drierite) was also maintained at this
temperature. Relative humidity and temperature values were obtained with a Rotronic Hygroskop (Rotronic AG). A sample of capsules (approx. 1000) was placed in a convection oven overnight at 55° ± 2°C. Samples were placed in humidity chambers and allowed to equilibrate for a minimum of one week prior to testing. Equilibration was considered obtained

after constant relative humidity values were obtained for three consecutive days.

Differential Scanning Calorimetry (DSC)

DSC thermograms were produced using a Perkin-Elmer DSC-4 differential scanning calorimeter interfaced with a Model 3600 thermal analysis data station (TADS) system. Samples of capsules weighing 5-6 mg $\pm$ 0.1 mg were prepared in aluminum sample dishes and scanned at 20 °C/min. Glass transition temperatures were determined on the first derivative curve. Comparison of thermogram data was made on samples normalized on a per mg basis. Samples of capsules were stored for 24 hours at 35°, 75° and 21° (35% RH).

Compression Testing

Capsules were compressed on a Chatillon motorized test stand equipped with a DDP 25Kg x 250 gm force gauge (Johnson Scale Co.). The force gauge was fitted with a flat 1.5" diameter circular plate. The platform was traversed its full distance and the circular plate was set 1mm from the platform surface. Platform travel speed was set at 8 (approximately 20cm/min).

Determinations

Accurately weighed samples (nearest 0.1 mg) of capsules weighing between 1 and 2 gm were placed in a preweighed porcelain crucible predried to a constant weight. After subtracting the weight of the crucible, the initial weight was recorded as wet weight. Samples were dried in a muffle furnace (Thermolyne) for 17 hours at 105°C. After drying,

the samples were placed in a desiccator for five minutes to allow samples to cool. Upon cooling to room temperature, the sample was reweighed. The crucible weight was subtracted, and the weight recorded as dry weight. The percent moisture was calculated as follows:

$$\% \text{ moisture} = \frac{\text{wet weight} - \text{dry weight} \times 100}{\text{wet weight}}$$

RESULTS AND DISCUSSIONS

The moisture content of capsule ranges from 13-16% w/w due to the characteristics of the raw gelatin. The data presented in Table 2 indicate that capsules adsorb and desorb moisture dependent upon the storage environment. No difference in percent relative humidity(%RH) or percent loss on drying (L.O.D.) was observed between the ADE and EBW capsule formulations. During the capsule filling operation, a room temperature of 20-25°c and a relative humidity between 45% and 55% is recommended by capsule manufacturers for optimum capsule filling performance. Below this humidity range, capsules become brittle and filling becomes problematic because of excessive capsule fracture.

From our working experience, it had been noted that ADE formulated capsules are more brittle than EBW formulated capsules and are more sensitive to operation room conditions i.e. temperature and humidity. However, the data in Table 2 and the sorption isotherms for ADE and EBW formulated capsules presented in Figure 1 did not appear to support this conclusion. Water in gelatin

TABLE 2. Relative Humidity and Loss on Drying of Capsules Equilibrated with Saturated Salt Solutions

Solute of Saturated Salt Solution	% RH of Chamber[1]	% Relative Humidity[1,2] Capsule Formulation		% L.O.D. Capsule Formulation	
		ADE	EBW	ADE	EBW
Drierite[3]	0.1	0.3	0.2	3.90	3.84
Lithium Chloride	8.0	11.3	11.2	6.54	6.65
Potassium Acetate	21.8	21.1	21.3	8.66	8.92
Calcium Chloride	27.3	22.5	20.5	9.68	9.66
Potassium Carbonate	43.2	42.7	43.5	12.50	12.67
Sodium Dichromate	52.1	52.0	52.0	13.50	13.31
Fresh Undried		48.0	39.5	13.96	14.90

[1]Determined at 22° ± 0.5°C.

[2]Values reported are the average of four determinations on a sample population of 20–30 capsules

[3]Anhydrous calcium sulfate, 20–40 mesh

capsules plasticizes capsules and therefore we anticipated a greater water content for EBW capsule compared to ADE capsules. Furthermore, ADE capsules contain a higher level of solids than EBW capsules on a per weight basis; 5.46% vs 1.82% respectively. It was therefore expected that ADE capsules would have a lower L.O.D. than EBW capsules.

We evaluated capsule brittleness as a function of temperature. Capsules were dried for 24 hours at various temperatures and subjected them to a fracture test. Capsule manufacturers utilize proportion tests to characterize the qualitative performance of capsules for their quality control. Typically, a sample of 400 capsules is placed in a pan in sample lots of 100 capsules and compressed at a predetermined applied force[4]. Capsules are then evaluated for fractures and shatters. Fractures are defined as capsules that have cracked or broken but remain intact. Shatters are defined as capsules that have completely disintegrated into small pieces. Acceptance of a batch of capsules is thus based on the number of fractures and shatters observed, e.g. accept for eight or less total fractured and shattered capsules in a 400 capsule sample; rejection for nine or more total fractured and shattered capsules in a 400 capsule sample.

For our study and for evaluating pharmaceutical capsules monitored on stability, this test design was deemed undesirable for the following reasons: (1)sample size was seen as being unacceptably high; (2)the pass-fail criteria limits the utility of the data because it does not provide a target specification range; (3)only a qualitative comparison and not a quantitative comparison could be made between the

TABLE 3. Comparison of Capsules Stored at Varying Temperatures

Storage Condition Temp (°C)[1]	x Applied Compression Force (Kg)[2]		Number of Fractures[3]		Number of Shatters[3]	
	ADE	EBW	ADE	EBW	ADE	EBW
21°[4]	6.65 (.09)	6.53 (.25)	1/20	2/20	0/20	0/20
35°	2.33 (.15)	5.43 (.93)	0/20	3/20	20/20	8/20
45°	2.12 (.13)	2.46 (.95)	0/20	0/20	20/20	20/20
55°	1.78 (.11)	1.78 (.14)	0/20	0/20	20/20	20/20
75°	1.34 (.09)	1.26 (.17)	0/20	0/20	20/20	20/20

[1] Stored 24 hours in convection oven at reported temperature ± 1°C. Relative humidity not monitored except where noted.

[2] Average of 20 capsules. Number in parenthesis is sample variance, S^2.

[3] Sample of 20 capsules compressed.

TABLE 4. Compression of Capsules Stored at Varying Relative Humidities at 23°C

% RH (22°C) of Capsules	x Applied Compression Force (Kg)[1]		Number of Fractures[2]		Number of Shatters[2]	
	ADE	EBW	ADE	EBW	ADE	EBW
0	1.2	1.2	0/20	0/20	20/20	20/20
9	2.30 (0.36)	4.31 (1.13)	0/20	0/20	20/20	20/20
21	4.88 (2.07)	5.98 (0.48)	11/20	1/20	5/20	1/20
29	5.45 (.08)	5.49 (.06)	3/20	0/20	1/20	0/20
43	6.18 (0.30)	6.25 (0.20)	1/20	0/20	0/20	0/20
52	5.90 (0.30)	5.96 (0.21)	0/20	0/20	0/20	0/20

[1]Average of 20 capsules. Number in parenthesis is sample variance.

[2]Sample of 20 capsules compressed.

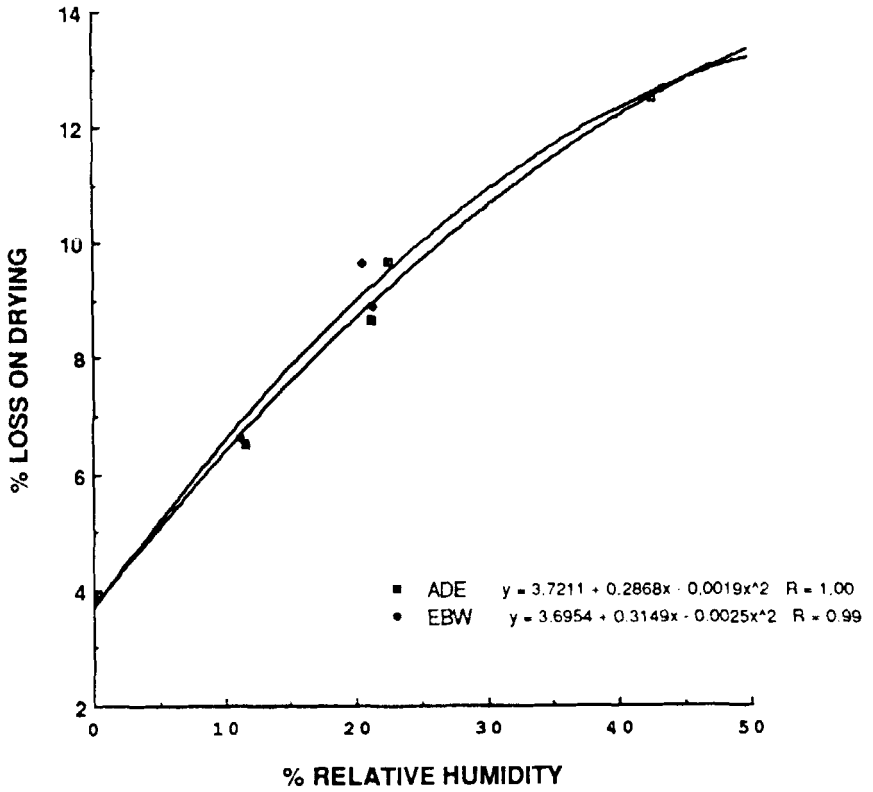

FIGURE 1

effects different capsule formulations exert on capsule shells, e.g. desiccate or hydrate the capsule shell.

A capsule brittleness test was designed utilizing a compression tester that yielded a valued response that quantified applied force (kg). The compression gauge used was a push-pull strain gauge mounted on a stand equipped with a movable platform that provided a constant applied force.

Resistance to the applied force was recorded on the strain gauge. A predetermined fixed speed and travel

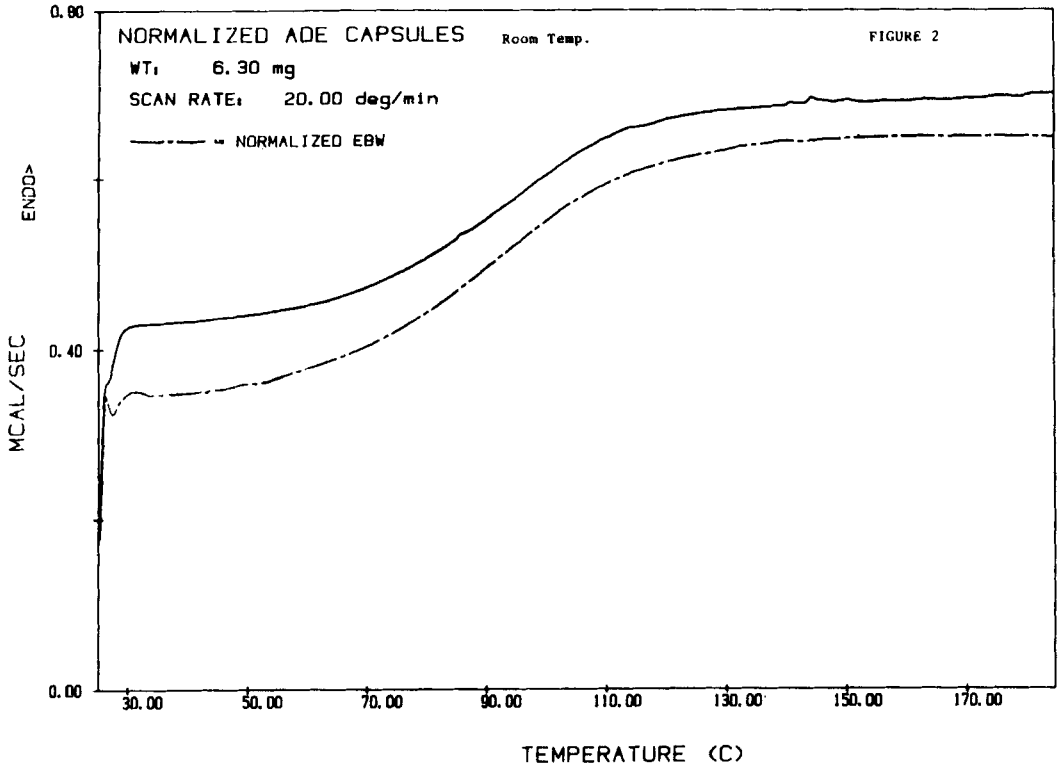

FIGURE 2

distance limited the total force applied and provided reproducible results. Capsules placed on the platform offered resistance quantified by the compression gauge. Brittle capsules provided less resistance than nonbrittle capsules and thereby registered a lower applied force.

Capsules were dried for 24 hours at various temperatures and subjected to the aforementioned compression test. The applied force and number of fractures and shatters are shown in Table 3. ADE and EBW capsules stored at room temperature conditions did

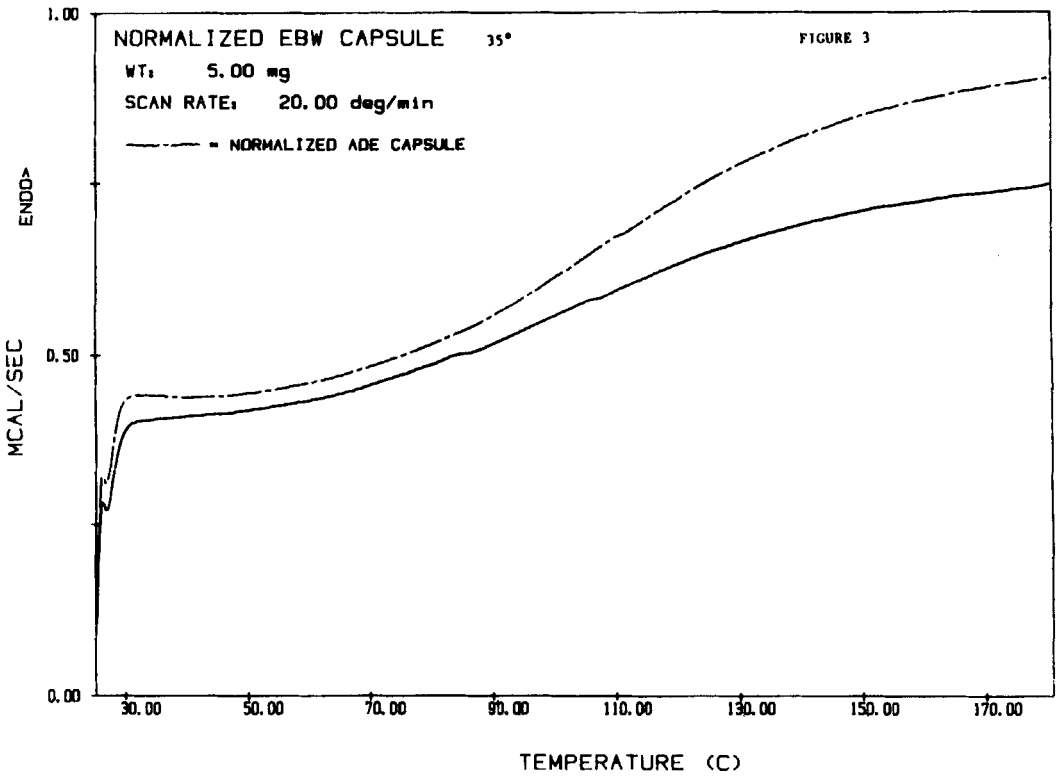

FIGURE 3

not shatter at the maximum applied force (approximately 6.6 kg) and 7.5 % of the capsules sampled fractured. As capsules were exposed to higher temperature stress conditions, the frequency of fractures and shatters increased. At temperatures of 45°C or above, 100% of the capsules sampled shattered.

An inverse relationship between increasing temperature and applied force necessary to cause capsule fracture was evident. At 35°C, ADE and EBW formulated capsules differentiated in their performance in the subjected test. ADE capsules were determined to be more

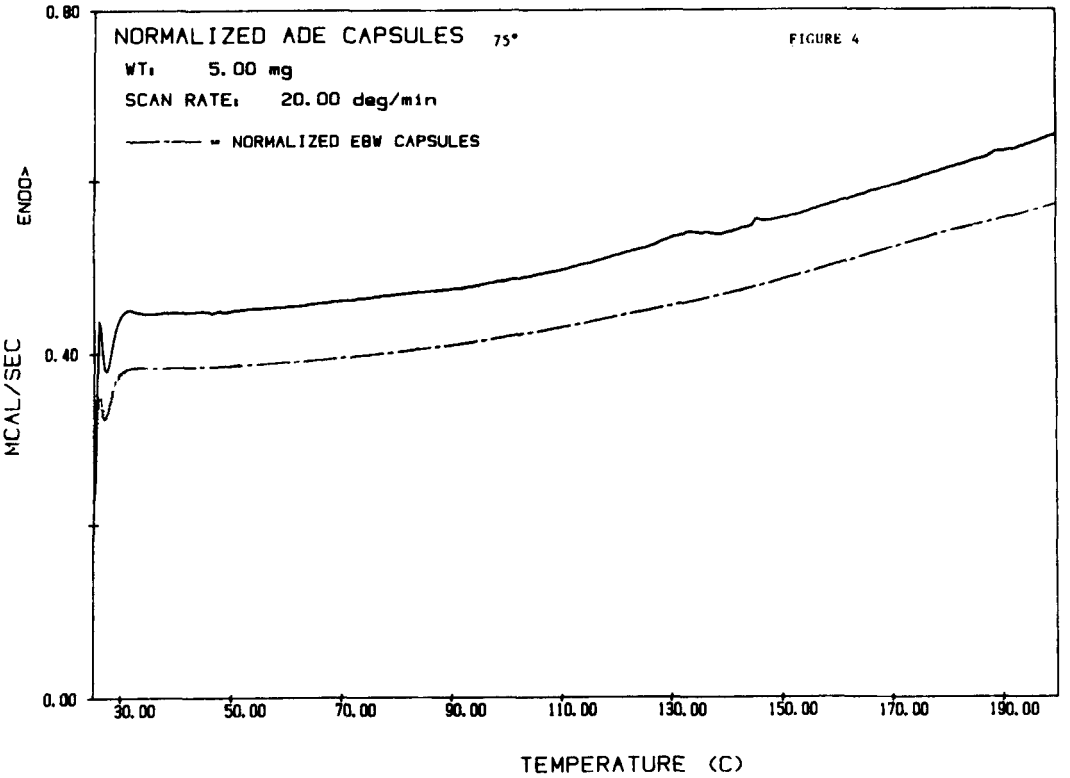

FIGURE 4

brittle than EBW capsules as noted by the greater number of shatters (20 verses 8 respectively) and by the applied compression force necessary to effect the shatter. EBW capsules stored at 35°C withstood an applied force of more than twice that necessary to shatter ADE capsules. It thus appears that the total volatile content calculated by L.O.D. was the same for ADE and EBW formulated capsules, but the temperature at which the volatiles were lost varied.Capsules were dried overnight and hydrated in constant humidity chambers of

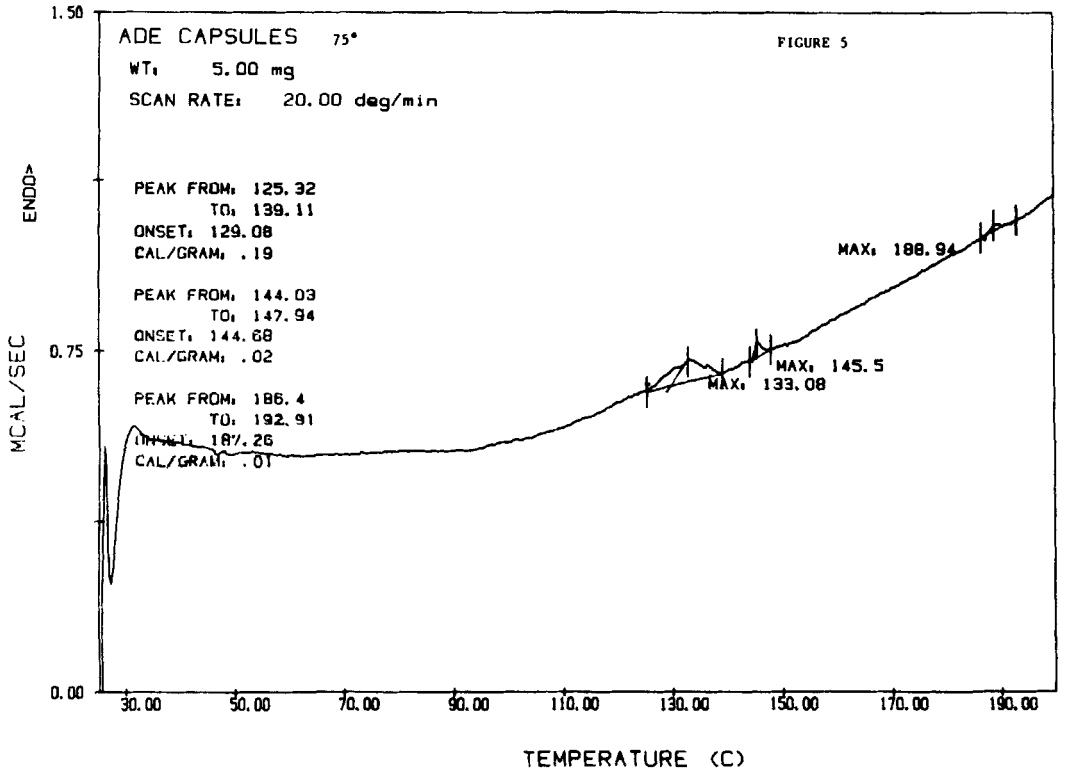

FIGURE 5

different relative humidities. Capsules were allowed to equilibrate and were subjected to the compression test. Capsules equilibrated to less than 43% RH fractured or shattered with the proportion of shatters increasing as relative humidity decreased. An applied force maxima was observed at approximately 45% relative humidity. The critical relatively humidity, defined as that relative humidity at which capsules become unuseable[5], was lower for EBW than ADE formulated capsules.

Capsules stored overnight at room temperature, 35°C and 75°C were subjected to differential scanning

calorimetry (DSC). At room temperature, ADE and EBW capsules displayed glass transitions at 89.5°C and 88.9°C (T_G from 50-120°C) respectively (Figure 2). At 35°C, ADE and EBW capsules displayed glass transition at 97.9°C and 97.5°C (T_G from 50-150°C) respectivley indicative of a loss in plasticity and increased brittleness (Figure 3).

At 75°C both ADE and EBW capsules displayed no glass transition (Figure 4) and ADE capsules displayed peak maxima at 133°C, 145.5°C and 188.9% indicating crystal growth within the capsule(Figure 5). EBW capsules did not display peak maxima through the temperature range scanned.

It can be concluded from these studies that hard gelatin capsules become brittle when exposed to elevated temperatures or reduced humidity. Dried capsules can be plasticized by hydrating them in elevated humidity chambers. The simple compression test developed hereinbefore is able to discriminate brittle from nonbrittle capsules and provide quantitative measures of these physical conditions.

This test can therefore provide a means of assessing the effects of temperature, humidity and long term stability on hard gelatin capsules.

ACKNOWLEDGEMENTS

The authors wish to thank R. DiGregorio for his technical assistance and J. Lanza for typing the manuscript.

REFERENCES

1. "General Specifications for CAPSUGEL Hard Gelatin Capsules", Capsugel Technical Report, 1985, pages 1-10.

2. "Capsule Technical Information Manual", Elanco Products, 1979, pages 7-11.

3. "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics", Center for Drugs and Biologics, Food and Drug Administration, Department of Health and Human Services, February 1987, page 14.

4. "Capsule Fracture Test Procedure", Elanco Products, personal communication, 1989.

5. M. Kaplow, Moisture Verses Dry Foods: Key to Effective Packaging, Package Eng., Sept. 1959.