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Physical-mechanical properties of film-coated soft gelatin capsules

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Abstract

Soft gelatin capsules containing ibuprofen dissolved in either PEG 400 or Miglyol® 812 were coated with an aqueous dispersion of Eudragit® L 30 D-55 using a Mini Hi-Coater. The physical-mechanical properties of the coated capsules, including tensile strength, Young's modulus and tensile toughness, were determined using a Chatillon DFGS50 force gauge attached to a Chatillon TCD-200 motorized test stand. The diametral compression tests were conducted at a rate of 12.7 mm/minute. Force-deflection curves were obtained and mathematically manipulated to yield stress-strain diagrams. The influence of two plasticizing agents, triethyl citrate (TEC) and tributyl citrate (TBC), on the physical-mechanical properties was determined. The hydrophilic plasticizer TEC was found to be the best plasticizer for the acrylic films, regardless of the fill liquid. The physical-mechanical properties of the coated and uncoated soft gelatin capsules were a function of the fill liquid. Temperature and humidity were found to influence the physical-mechanical properties of the coated capsules. The adhesion between the gelatin capsule and the acrylic polymer was found to be dependent on both the fill liquid and plasticizer in the coating formulation. Coating dispersions plasticized with TEC exhibited good adhesion with both the PEG 400 and the Miglyol® 812, whereas the TBC plasticized film coating showed good adhesion with the Miglyol® 812 fill liquid. The acrylic film coatings for the PEG-containing capsules and plasticized with TBC exhibited an increased adhesion of the polymer to substrate over time when stored at both high temperature and high humidity.

Keywords: Soft gelatin capsule; Enteric; Acrylic resin copolymer; Adhesion; Physical-mechanical

1. Introduction

The formulation of drugs into soft gelatin capsules has gained popularity over the last several years due to the many advantages of this dosage form. The bioavailability of hydrophobic drugs can be significantly increased when formulated into a soft gelatin capsule (Mallis et al., 1975, Johnson et al., 1976). Many problems associated with tableting, including poor compaction and lack of content or weight uniformity, can be eliminated when a drug is incorporated into this dosage form (Seager, 1985). Improved stability of drugs that are highly susceptible to oxidation and hydrolysis can be achieved when formulated into a soft gelatin capsule (Maconachie, 1977, Ebert, 1977).

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Solid dosage forms containing drugs that are susceptible to degradation in the stomach due to the acidic environment or gastric enzymes have been stabilized with an enteric film coating. A decrease in gastric irritation can also be achieved by enterically coating the solid dosage form (Petroski, 1989). Enteric polymers, including the acrylates, cellulosic derivatives and shellac, have previously been used to coat tablets (Lehmann, 1986, Porter and Ridway, 1982) and pellets (Mehta et al., 1986). Several studies have addressed the enteric coating of hard gelatin capsules (Murthy et al., 1986, 1988, Thoma and Bechtold, 1986). Few studies, however, have focused on the enteric coating of soft gelatin capsules (Felton et al., 1995).

Adhesion between a polymer and a substrate is a major factor to consider when film coating a solid dosage form (Rowe, 1977). Several researchers have investigated the variables that influence the adhesion of a polymer to the surface of a tablet during a film coating operation (Stanley et al., 1981, Wood and Harder, 1970, Fisher and Rowe, 1976, Nadkarni et al., 1975). Okhamafe and York, 1985 reported that complete loss of adhesion between a film coat and a tablet would retard the ability of the coating to provide mechanical protection to the dosage form. Accumulation of moisture at the film-tablet interface may occur as a result of decreased adhesion, causing significant stability problems for drugs susceptible to hydrolysis. Thoma and Bechtold, 1986 reported that adhesion problems with coating hard gelatin capsules could be overcome with an aqueous subcoat of hydroxypropyl methylcellulose.

Traditional methods for evaluating the stability and efficiency of film-coated solid dosage forms have consisted primarily of following changes in the dissolution properties of the coated product during storage. Basic research with both solvent- and aqueous-based polymeric dispersions has focused on the physical-mechanical properties of free films including tensile strength and elongation. These physical-mechanical data have been used to make predictions regarding the long-term storage stability of film-coated solid dosage forms. The physical-mechanical testing of free films has been used to evaluate the effectiveness of plasticizers (Sinko and Amidon, 1989), as well as the permeability of the film coating (Li and Peck, 1989) and also the incidence of film defects in the coated tablets, including edge splitting and bridging of the intangliations (Rowe, 1983).

The physical-mechanical properties of free films prepared from aqueous dispersions containing the acrylic resin copolymers have been addressed by many authors (Gutierrez-Rocca and McGinity, 1993, 1994, Obara and McGinity, 1994). Free films are generally prepared using a casting method, where the polymeric solution or dispersion is cast onto a smooth surface of Teflon® or aluminum and the water or solvent is slowly evaporated. Since the primary method of application of a polymeric solution or dispersion to a solid substrate is by spraying, a recent report in the literature compared the properties of sprayed films to cast films (Obara and McGinity, 1994). The differences between the two methods of film preparation were found to be polymer dependent.

Previous work which involved enterically coated soft gelatin capsules has shown that the fill liquid in conjunction with the plasticizer could significantly influence the disintegration properties of the final product (Felton et al., 1995). The objective of the current investigation was to study the physical-mechanical and adhesion properties of soft gelatin capsules following the application of an acrylic resin copolymer. A novel digital test gauge apparatus was used to conduct compression tests to determine tensile strength, Young's modulus and tensile toughness of the film-coated capsules. The effects of the physical and chemical properties of both the substrate and plasticizing agent on the physical-mechanical properties and the adhesion properties of the film coat to the substrate were investigated. The influence of storage conditions on the physical aging of the film-coated capsules was also studied.

2. Materials

Round soft gelatin capsules (size 7) were obtained from R.P. Scherer (Detroit, MI) and contained ibuprofen 200 mg dissolved in either

polyethylene glycol (PEG 400, Union Carbide, Houston, TX) or Miglyol® 812 (Dynamit-Nobel, Troisdorf, Germany). The average weight ($n = 20$) of the uncoated capsules containing PEG 400 was 0.557 g. Uncoated capsules containing Miglyol® 812 weighed 0.533 g. The Eudragit® L 30 D-55 acrylic resin copolymer was donated by Rohm Tech (Malden, MA). The two plasticizers, triethyl citrate (solubility 6.5 g/100 ml water at 25°C) and tributyl citrate (insoluble in water at 25°C), were donated by Morflex Inc. (Greensboro, NC).

3. Methods

3.1. Coating procedure

The acrylic coating suspensions were prepared by adding water to the commercially available Eudragit® L 30 D-55 polymeric dispersion to decrease the solids content to fifteen percent. Twenty percent plasticizer (based on dry polymer weight) was added. The soft gelatin capsules were coated in a Mini Hi-Coater Model HCT-20, Fruend Company (Tokyo, Japan) using a method previously reported (Felton et al., 1995). A 300-g batch of soft gelatin capsules was placed in the Hi-Coater and prewarmed for 30 min prior to the initiation of spraying. The prewarming step was required to raise the temperature of the fill liquid to that of the bed temperature to allow for uniform drying of the polymeric dispersion. Outlet bed temperatures were held between 30°C and 32°C. The pan rotational speed was set at 35 rpm. Atomizing air pressure was 0.9 kg/cm^2. The plasticized Eudragit® L 30 D-55 dispersion was applied at a rate of 2.0 g/min. To promote further coalescence of the polymeric film and to assure that the distribution of the plasticizer was homogeneous, all capsules were equilibrated at 35°C for approximately 16 h after the acrylic coating was applied.

3.2. Physical analysis

Diametral compression testing was conducted on the coated soft gelatin capsules using a Chatillon DFGS50 digital force gauge attached to a Chatillon TCD-200 motorized test stand (Chatillon, Greensboro, NC), as shown in Fig. 1. The force gauge was fitted with a flat md diameter circular steel plate which served as the upper platen. Capsules were placed on a lower, stationary platen. The upper platen was lowered at a rate of 12.7 mm per minute. A personal computer (Leading Edge, Westborough, MA) recorded the force (kg), measured by the gauge, and the displacement (mm) every 0.02 mm that the platen moved. The force-deflection data were mathematically manipulated to obtain stress-strain curves. The stress was obtained by dividing the load by the initial cross-sectional area of the capsule. Although the area will change during a compression test, it is the most common stress that has been reported (Higdon et al., 1985). The strain was

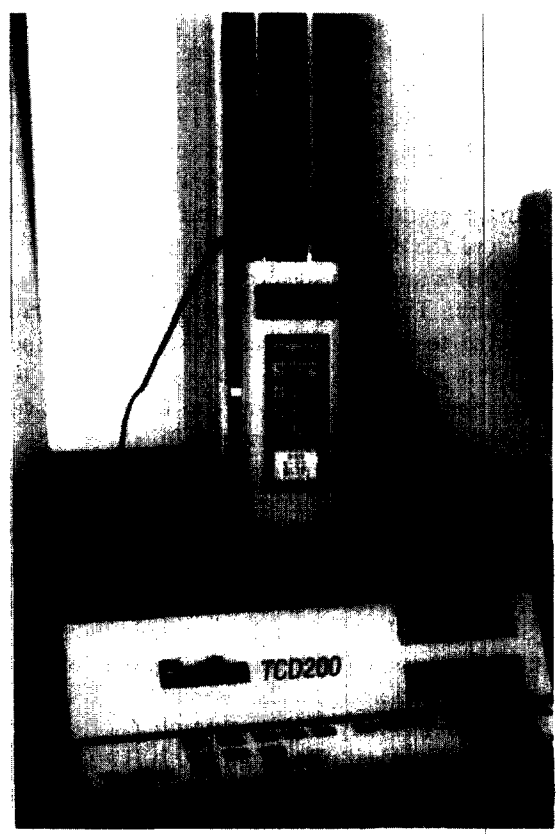

Fig. 1. Chatillon DFGS50 digital force gauge attached to a Chatillon TCD-200 motorized test stand for diametral compression tests.

calculated by dividing the change in length by the original length or the diameter of the coated capsule. The percent fracture strain (equivalent to percent elongation in tensile testing) was calculated. The tensile strength of the film at the fracture point was determined. The area under the stress-strain curve was calculated to obtain the tensile toughness of the film-coated capsule. Young's modulus was also calculated from the linear portion of the stress-strain curve. Six capsules from each lot were tested.

4. Results and discussions

Tensile testing of free films has been the traditional method used for studying the physical-mechanical properties of polymers. Compression tests have also been used, however, to a lesser extent. Many similarities exist between tension and compression tests, including the manner of conducting the test and the analysis and interpretation of the results (Dowling, 1993). In the current study, the compression testing of the coated soft gelatin capsules was conducted using a Chatillon digital force gauge and test stand. The force and the deflection were recorded on a computer (MPa and mm, respectively) during the test procedure. The data were then mathematically converted to stress and strain. The data obtained using this equipment were so complete that the failure point of both the film and the capsule can be determined, as shown in Fig. 2.

The results demonstrated that in most cases the gelatin shell and polymeric film fractured simultaneously, usually at the seam of the capsule, indicating good adhesion between the polymer and the gelatin. This is in agreement with the findings of Stanley et al., 1981 and co-workers who suggested that coated tablets which failed with a single peak had a high substrate/coating adhesion. In the current study, PEG-containing soft gelatin capsules coated with Eudragit® L 30 D-55 plasticized with TBC showed poor adhesion between the acrylic polymer and the capsule shell as evidenced by a fracture of the film, followed by fracture of the gelatin shell, probably due to higher internal stresses within the film coating (Fig. 2B).

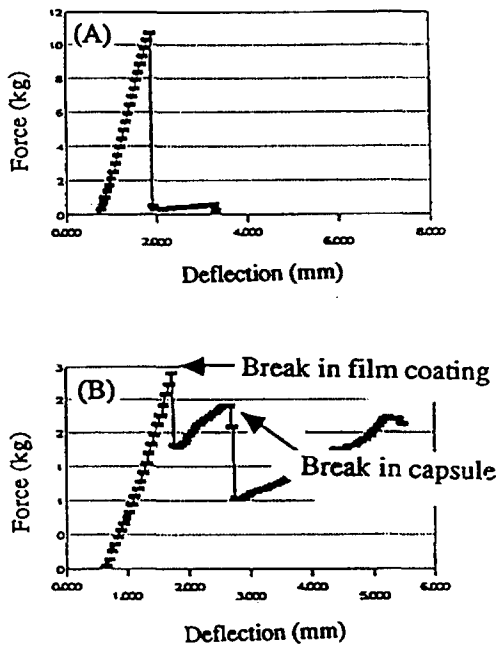

Fig. 2. Force-deflection profiles from a Chatillon DFGS50 digital force gauge of film-coated soft gelatin capsules containing PEG 400 (A) Eudragit® L 30 D-55 plasticized with TEC and (B) Eudragit® L 30 D-55 plasticized with TBC.

A previous report in the literature showed that the decreased adhesion between a polymer and tablet which occurred during storage at 37°C and 75% relative humidity (RH), was attributed to increased swelling-induced stresses at the film-tablet interface (Okhamafe and York, 1985). In the present study, however, the adhesion between the acrylic polymeric coating plasticized with TBC and the PEG-containing gelatin capsule was found to increase during storage at both high humidity and high temperatures, as indicated by the fracture point of the polymer and gelatin shell occurring at a single point. This result could be due to the migration of PEG 400 fill liquid through the gelatin shell and into the film coating to function as a plasticizing agent, thereby decreasing the internal stresses within the film coating. This result is in agreement with Thoma and Bechtold, 1986 who reported that increased adhesion between an acrylic polymer and hard gelatin capsules could be achieved by the addition of PEG 400 into the film coating formulation.

Table 1
Initial physical-mechanical properties of soft gelatin capsules coated with an enteric acrylic resin copolymer.

Fill liquid	Plasticizer	Tensile strength (S.D.)	Young's modulus (S.D.)	Tensile toughness (S.D.)
PEG 40	TEC	0.4055 MPa (0.023)	2.70 MPa (0.214)	760.41 MPa (61.8)
	TBC	0.2627 MPa (0.023)	3.029 MPa (0.340)	354.6 MPa (37.4)
Miglyol® 812	TEC	0.1323 MPa (0.023)	1.287 MPa (0.14)	179.57 MPa (18.6)
	TBC	0.0692 MPa (0.012)	1.318 MPa (0.146)	84.64 MPa (9.31)

The plasticizing agent in the film coating formulation was found to affect the physical-mechanical properties of the coated soft gelatin capsules, as shown in Table 1. The TEC was found to better plasticize the acrylic polymeric coating, as evidenced by a higher percent fracture strain, as seen in the initial stress-strain diagrams in Fig. 3. The tensile strength and tensile toughness of the TEC plasticized coated capsules were significantly greater than the TBC plasticized coated soft gelatin capsules containing PEG 400 as the fill liquid. These results support the initial findings in our laboratories that showed TBC plasticized coated soft gelatin capsules containing PEG 400 fill liquid did not exhibit initial enteric protection (Felton et al., 1995).

The physical-mechanical properties of the Miglyol®-containing soft gelatin capsules were not found to be as strongly influenced by the plasticizer in the film coating as the PEG-containing capsules, as shown in Fig. 3. One possible explanation for these results could be due to the solubility parameters. The solubility parameter of the TBC, as calculated by the Van Krevelen method (Van Krevelen, 1976), was found to be similar to that of PEG 400 and Miglyol® 812, whereas the solubility parameter of TEC was found to be much greater than Miglyol® 812, as shown in Table 2. The TEC-plasticized coated capsules containing Miglyol® 812 exhibited a higher percent fracture strain, demonstrating that TEC was a better plasticizer for the polymer. This result is in agreement with previous findings that Miglyol®-containing soft gelatin capsules coated with Eudragit® L 30 D-55 plasticized with TEC provided better enteric protection than the TBC plasticized film coating (Felton et al., 1995).

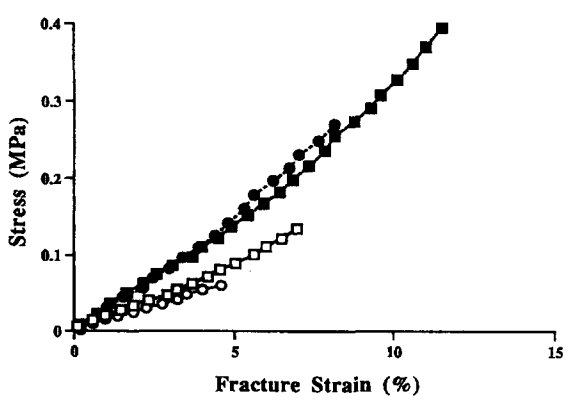

Fig. 3. Initial stress-strain diagrams of soft gelatin capsules coated with Eudragit® L 30 D-55 (□) Miglyol® 812 fill liquid/TEC plasticizer, (■) PEG 400 fill liquid/TEC plasticizer, (○) Miglyol® 812 fill liquid/TBC plasticizer and (●) PEG 400 fill liquid/TBC plasticizer.

The stress-strain diagram shown in Fig. 3 also demonstrates the significant influence the fill liquid of the soft gelatin capsules exerted on the physical-mechanical properties of the coated soft gelatin capsules. The PEG-containing coated capsules exhibited higher Young's modulus, tensile strength, and tensile toughness than the Miglyol®-containing coated capsules, regardless of the plasticizer incorporated into the film coating. Stronger and tougher films were obtained when the acrylic

Table 2
Solubility parameters[a] of plasticizers, fill liquids and polymer

Solubility parameter	$(J/cm^3)^{1/2}$
Eudragit® L	23.0
Triethyl Citrate	21.1
PEG 400	19.7
Tributyl Citrate	19.5
Miglyol® 812	16.0

[a]as calculated per Van Krevelen method (Van Krevelen, 1976)

polymer was coated on the soft gelatin capsules containing PEG 400. These results demonstrated that the inherent compressibility of the uncoated soft gelatin capsules containing either Miglyol® 812 or PEG 400 affected the physical-mechanical properties of the film-coated soft gelatin capsules.

Changes in the physical-mechanical properties of the film-coated capsules were followed over time as a function of temperature and relative humidity. Within 2 weeks of storage at 40°C/75% RH, all capsules, irrespective of fill liquid or plasticizer, agglomerated and were unable to be tested, due to the absorption of water into the film coating. The plasticizing effect from the moisture resulted in a lowering of the glass transition temperature (Tg). These results are in agreement with those of Gutierrez-Rocca and McGinity, 1994 who found that the Tg of the acrylic polymer decreased during storage at high humidity due to adsorbed water acting as a plasticizer and breaking the intermolecular hydrogen bonds of the polymer, which resulted in a more elastic film. During storage at room temperature and 75% RH, all formulations of the coated capsules were more flexible, as evidenced by a higher tensile strength and tensile toughness and a lower Young's modulus. These results may also be attributed to the migration of water molecules into the film coating to plasticize the polymer and to lower the Tg.

All capsules, regardless of fill liquid or plasticizer, exhibited an increase in Young's modulus during storage at 0%RH/RT, as shown in Fig. 4, demonstrating that the film coating became increasingly more brittle and less able to deform under external stress. Interestingly, for the capsules containing the Miglyol® 812 fill liquid, the Young's modulus was found to be dependent on the plasticizer incorporated in the coating formulation, whereas the PEG-containing capsules exhibited similar elastic moduli, regardless of the plasticizer in the polymer. One possible reason for these results could be that the PEG 400 fill liquid migrated into the film coating to further plasticize the films. These films, therefore, became less dependent on the plasticizer incorporated in the coating formulation.

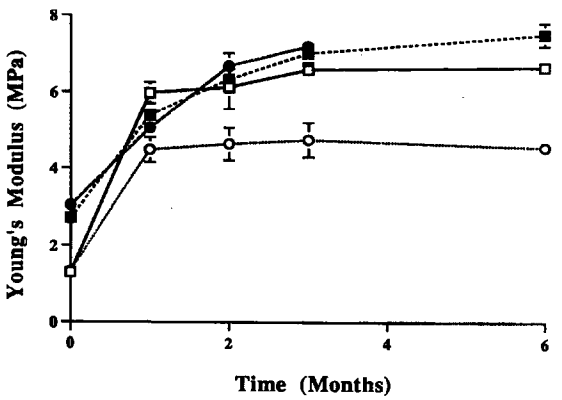

Fig. 4. Influence of fill liquid and plasticizer in the film coating on the Young's Modulus of soft gelatin capsules coated with Eudragit® L 30 D-55 during storage at 0%RH/RT (□) Miglyol® 812 fill liquid/TEC plasticizer, (■) PEG 400 fill liquid/TEC plasticizer, (○) Miglyol® 812 fill liquid/TBC plasticizer and (●) PEG 400 fill liquid/TBC plasticizer; (crack formation occurred in the TBC plasticized PEG-containing capsules and were unable to be tested at 6 months).

The tensile strength of the coated capsules was followed during storage at 0% RH/RT and was found to increase, irrespective of the fill liquid or plasticizing agent, as shown in Fig. 5. The percent fracture strain was found to decrease over time

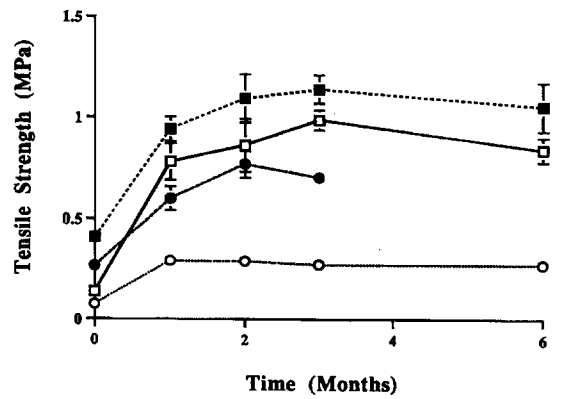

Fig. 5. Influence of fill liquid and plasticizer in the film coating on the tensile strength of soft gelatin capsules coated with Eudragit® L 30 D-55 during storage at 0%RH/RT (□) Miglyol® 812 fill liquid/TEC plasticizer, (■) PEG 400 fill liquid/TEC plasticizer, (○) Miglyol® 812 fill liquid/TBC plasticizer and (•) PEG 400 fill liquid/TBC plasticizer; (crack formation occurred in the TBC plasticized PEG-containing capsules and were unable to be tested at 6 months).

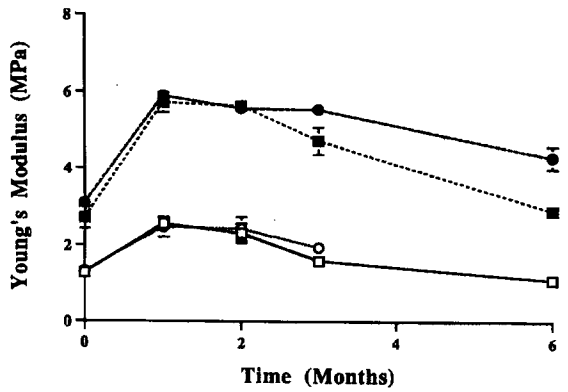

Fig. 6. Influence of fill liquid and plasticizer in the film coating on the Young's Modulus of soft gelatin capsules coated with Eudragit® L 30 D-55 during storage at 40°C. (□) Miglyol® 812 fill liquid/TEC plasticizer, (■) PEG 400 fill liquid/TEC plasticizer, (○) Miglyol® 812 fill liquid/TBC plasticizer and (•) PEG 400 fill liquid/TBC plasticizer; (crack formation occurred in the TBC plasticized Miglyol®-containing capsules and were unable to be tested at 6 months).

during storage at 0% RH/RT. These effects were attributed to a decrease in water content of the polymeric film under these storage conditions. The film coatings became strong and brittle during storage at these conditions. These results are supported by Gutierrez-Rocca and McGinity, 1994 who demonstrated that the water content

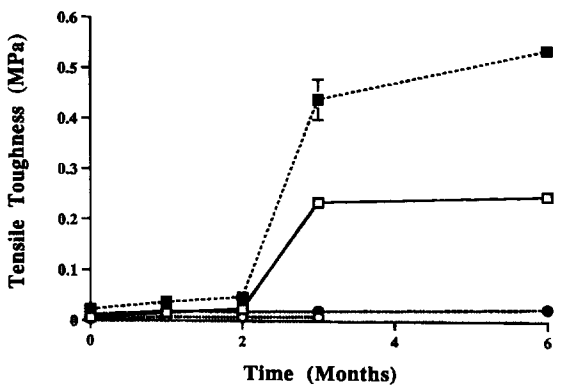

Fig. 7. Influence of fill liquid and plasticizer in the film coating on the tensile toughness of soft gelatin capsules coated with Eudragit® L 30 D-55 during storage at 40°C (□) Miglyol® 812 fill liquid/TEC plasticizer, (■) PEG 400 fill liquid/TEC plasticizer, (○) Miglyol® 812 fill liquid/TBC plasticizer and (•) PEG 400 fill liquid/TBC plasticizer; (crack formation occurred in the TBC plasticized Miglyol®-containing capsules and were unable to be tested at 6 months).

within an acrylic film decreased during storage at low relative humidity. Verhoeven et al., 1989 also reported that the water present in a polymeric film would function as a plasticizer.

The Young's modulus was found to increase initially for all capsules, regardless of plasticizer, during storage at 40°C, as shown in Fig. 6. For longer time periods, however, the modulus of elasticity for both the Miglyol®-and PEG-containing capsules decreased. The effects were more dramatic for those capsules plasticized with TEC for both fill liquids. Tensile toughness, a measure of the ability of the polymer to absorb energy without fracture, remained constant during storage at 40°C, for the capsules that were coated with the TBC plasticized acrylic resin, irrespective of the fill liquid, as shown in Fig. 7. The TEC plasticized film-coated capsules, however, exhibited dramatic increases in tensile toughness during storage at the elevated temperature. The decrease in Young's modulus and increase in tensile toughness could be due to an increase in the free volume of the polymer. During storage at high temperature, an increase in molecular motions occur within the polymer chains which permit the chains to orient themselves parallel to the direction of flow during the compression test which would result in tougher, more ductile behavior. These results indicate the TEC was a better plasticizer for the Eudragit® L 30 D-55 film coatings, regardless of fill liquid.

In conclusion, the Chatillon equipment with the digital force gauge has been shown to be a useful tool for determining the physical-mechanical properties, including tensile strength, Young's modulus and tensile toughness, of film-coated capsules. This equipment was also shown to yield useful information regarding the adhesion characteristics of the coated soft gelatin capsules. The current study demonstrated that the hydrophilic plasticizer TEC better plasticized the acrylic polymer than the hydrophobic TBC, regardless of the fill liquid contained within the soft gelatin capsule. The coated capsules containing the fill liquid Miglyol® 812 exhibited a lower Young's modulus and tensile strength than the PEG-containing coated capsules, irrespective of the plasticizer incorporated into the film coating. The Young's

modulus and tensile strength of the coated capsules were found to increase during storage at low humidity, regardless of the plasticizing agent in the film, whereas storage at high temperature resulted in tougher, more ductile behavior of the TEC plasticized film-coated capsules. The current study demonstrated that stronger, tougher film-coated capsules resulted during storage at elevated humidity. Adhesion between the enteric polymer and the gelatin shell was found to be dependent on the plasticizer incorporated into the coating formulation and the fill liquid of the soft gelatin capsule. An increase in adhesion between the PEG 400-containing capsules and the TBC-plasticized Eudragit® L 30 D-55 polymer during storage suggested a migration of the PEG 400 fill liquid into the film coating.

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