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Physical and enteric properties of soft gelatin capsules coated with Eudragit® L 30 D-55

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Abstract

The enteric coating of soft gelatin capsules (SGC) containing ibuprofen in either PEG 400 or Miglyol® was investigated. The effects of two plasticizers, triethyl citrate (TEC) and tributyl citrate (TBC), on the physical and enteric properties of SGC coated with Eudragit® L 30 D-55 were studied. The water soluble plasticizer TEC was found to be a good plasticizing agent for the Eudragit® L 30 D-55 irrespective of the fill liquid, while the TBC provided satisfactory results only for capsules containing the hydrophobic fill liquid, Miglyol®. The combination of TEC and TBC provided effective plasticization for the acrylic coating regardless of the fill liquid. A subcoat of HPMC showed no effect on the enteric protection of either Miglyol®- and PEG-containing capsules that were stored at room temperature and zero percent relative humidity. The moisture content of the gelatin shell of the film coated SGC stored at room temperature and at 0 or 96% relative humidity was followed as a function of time. The load strength of the capsules was measured during 3 months of storage using an Instron universal testing apparatus, and the physical-mechanical properties of the capsules were correlated with the moisture content of the SGC. As the moisture content of the gelatin decreased, all formulations exhibited an increase in load strength.

Keywords: Soft gelatin capsule; Enteric coating; Eudragit® L copolymer; Plasticizer; PEG 400; Miglyol®; Mechanical properties

1. Introduction

For drugs that are susceptible to degradation in the stomach due to the presence of enzymes or acidic media, protection of the dosage form has generally been achieved through the application of an enteric polymer. Enteric polymeric coatings have also been employed to decrease the incidence of gastric irritation from drugs such as aspirin (Petroski, 1989) and to deliver drugs to the small intestine (Sherif et al., 1969). Such polymers include the acrylates, cellulosic derivatives, and shellac. These polymers have been used previously for enteric coating of tablets (Porter et al., 1982; Lehmann, 1986) and pellets (Mehta et al., 1986)).

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Few studies, however, have reported on the coating of gelatin capsules with enteric polymers. Murthy and co-workers (1986) conducted a comparative evaluation of the aqueous enteric polymers, Eudragit® L 30 D, Aquateric®, and Coateric®, coated on hard gelatin capsules (HGC). Higher levels of enteric coatings were needed to prevent agglomeration of capsules stored at high temperatures and humidity. No significant difference in release rates or enteric protection was found between the two plasticizers, diethyl phthalate (DEP) and triethyl citrate (TEC), in the Eudragit® coatings. The Eudragit® L 30 D showed excellent stability with no change in dissolution properties over time. Murthy and co-workers (1988) also investigated the effect of hydroxypropyl cellulose (HPC) subcoats and overcoats on organic and aqueous-based enteric polymers. Eudragit® L 30 D was found to provide a smooth homogeneous film with and without the HPC subcoat with no difference noted in enteric protection.

Thoma and Bechtold (1986) reported that problems which occur during the enteric coating of hard gelatin capsules were generally due to the physical properties of the gelatin. Film coating HGC with aqueous spray formulations caused the capsule shell to soften and become sticky due to solubilization of the gelatin. The application of HPC or HPMC (hydroxypropyl methylcellulose) as a subcoat was found to eliminate the problem, though an increase in brittleness of the gelatin capsule due to water evaporation and drying was reported. The addition of PEG 400 and PEG 6000 to the coating formulation was found to provide improved adhesion of the polymer to the gelatin shell.

The formulation of drugs into soft gelatin capsules (SGC) has been reported to solve many problems associated with tableting, including poor compaction, lack of content or weight uniformity, and other powder flow or mixing problems (Seager, 1985). Improved stability has been achieved through the use of soft gelatin capsules, most notably with drugs which are highly susceptible to oxidation and hydrolysis (Ebert, 1977; Maconachie, 1977). However, the greatest advantage that SGC offer is the increased bioavailability of hydrophobic drugs (Mallis et al., 1975; Johnson et al., 1976). Coating SGC with enteric polymers would allow formulations of drugs which are sensitive to low pH or gastric enzymes to benefit from the advantages that SGC offer. However, the inherent flexibility of the gelatin shell presents significant challenges to the pharmaceutical scientist when film coating soft gelatin capsules with enteric polymers. The objectives of the present study were to investigate the effects of plasticizers and the fill liquid on the physical and enteric properties of soft gelatin capsules that were coated with Eudragit® L 30 D-55 (known as Eudragit® L 30 D prior to 1 July 1993). The stability of the enteric coated SGC and the moisture content of the gelatin were also studied during storage as a function of humidity.

2. Materials and methods

2.1. Materials

The soft gelatin capsules were obtained from R.P. Scherer (Detroit, MI) and contained ibuprofen 400 mg dissolved in either polyethylene glycol (PEG 400, Union Carbide, Houston, TX) or Miglyol® 812 (Dynamit-Nobel, Troisdorf, Germany). The soft gelatin capsules were size 6 oblong (II). The final weight of the uncoated capsules containing PEG was approx. 0.721 g. Uncoated capsules containing the Miglyol® weighed on average 0.643 g. The Eudragit® L 30 D-55 was donated by Rohm Tech (Maiden, MA) and Opadry® was donated by Colorcon, Inc. (West Point, PA). The two plasticizers, triethyl citrate and tributyl citrate, were donated by Morflex Inc. (Greensboro, NC).

2.2. Methods

2.2.1. Coating preparation

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 approx. 15%. 20% plasticizer (based on dry polymer weight) was added, and the suspensions were agitated for at

least 30 min for dispersions containing the water soluble plasticizer (TEC), and for a minimum of 48 h for the suspensions containing the non-water soluble plasticizer (TBC).

A 2% solution of hydroxypropyl methylcellulose (HPMC) was prepared by adding the Opadry® to purified water. A clear solution was obtained following agitation for approx. 2 h.

2.2.2. Coating procedure

Soft gelatin capsules containing ibuprofen solutions were coated in a Mini Hi-Coater Model HCT-20, Fruend Company, Tokyo, Japan. A 300 g batch was placed in the Hi-Coater and prewarmed for 30–60 min before coating was initiated. Outlet bed temperatures were held between 30 and 34°C. The rotational speed was set at 35 rpm. Batches which were subcoated with HPMC were coated at a sprayed rate of 2.2 g/min and the air pressure was 1 kg/cm^2. The plasticized Eudragit® L 30 D-55 dispersion was applied at a rate of 2.1 g/min and the air pressure was 1 kg/cm^2. To promote further coalescence of the polymeric film and to ensure the distribution of plasticizer was homogeneous, all capsules were equilibrated for approx. 16 h at 35°C after the acrylic coating was applied (Goodhart et al., 1984; Lippold et al., 1989).

2.2.3. Disintegration test

Since ibuprofen is virtually insoluble in acidic media, and gelatin will dissolve within minutes in 0.1 N HCl, disintegration testing with a Bio-Dis II (VanKel Industries, Edison, NJ) was used to determine whether or not enteric protection had been achieved. The Bio-Dis II was programmed to operate at 20 dips per min in 250 ml 0.1 N HCl at 37°C. Three capsules from each lot were tested for enteric resistance.

2.2.4. Moisture analysis

The residual moisture in the capsules walls was determined with the Karl Fischer technique and from moisture loss on drying. A modification of the Karl Fischer method was used, in which the gelatin was placed in acetone and allowed to equilibrate for a 12 h period before the sample was placed in the apparatus. To determine loss on drying, soft gelatin capsules from each lot were cut longitudinally along the seam. The fill liquid was carefully removed and the capsules were dried with a laboratory wipe. The capsule shells were weighed, placed in a 40°C oven for 4 days, then reweighed. Weight loss and percent weight loss were then calculated ($n = 4$). Since there was less than a 1% difference in the results from both methods, and the Karl Fischer method took considerably more time to perform, the moisture content was determined using the loss on drying method.

2.2.5. Physical analysis

The mechanical properties of the SGC were measured using an Instron, Model 4201 universal testing apparatus. The capsule to be tested was placed on the lower stationary platform, and the upper platen was adjusted until it was in contact with the capsule. The upper platen was then activated to lower and compress the capsule at a rate of 5 mm/min. The load strength was measured in kg, and the distance the upper platen traveled in mm at the failure point of the soft gelatin capsule was recorded.

3. Results and discussion

Previous reports in the literature have addressed some of the problems concerning the film coating of hard gelatin capsules that are unique to that dosage form. The two-piece design of the HGC has caused problems in the film coating process, due mainly to the separation of the HGC during the coating process, resulting in the polymeric dispersion gaining entrance to the fill powder. Thoma and Bechtold (1986) suggested a number of procedures to minimize these problems. Soft gelatin capsules generally contain the medicament dissolved or dispersed in oils or hydrophilic liquids, which may present unique problems in the application of enteric polymers. In our study, the soft gelatin capsules were placed in the Hi-Coater and prewarmed before coating was initiated. Without this prewarming, the SGC were very cold to the touch after completion of the coating process and the outer layers of the coat-

ing dried faster than the inner coating layers, causing bubble formation in the film. Prewarming the capsules increased the temperature of the fill liquid to that of the bed temperature, and allowed the coating to dry more uniformly, resulting in a smooth, homogenous film.

The addition of a plasticizer in the polymeric film system was also necessary for the formation of smooth films that were free of cracks and other defects. Physical characteristics of the film such as tensile strength and elasticity will change with the addition of a plasticizer. Plasticizers are especially necessary components to reduce brittleness, improve flow, impart flexibility, and increase toughness, strength, and tear resistance of the film coat (Banker, 1966). The plasticizer must be distributed evenly between the polymer chains in order to disrupt the intermolecular forces holding the chains in a rigid pattern. Disruption of the polymer-polymer bonds generally results in a decrease in tensile strength, a lowering of glass transition temperature, and an increase in elongation and flexibility of the films. Use of a plasticizer has been found to be imperative when working with polymeric films, such as acrylic polymers, that are generally considered to be brittle in nature.

Two alkyl esters of citric acid, TEC and TBC, were used as plasticizers in the film coating formulations. The three butyl groups on the TBC caused this plasticizer to be inherently more hydrophobic than TEC. The method of plasticizer incorporation into an aqueous polymeric dispersion has been shown to be a crucial factor in determining the physical-mechanical properties of the final film coating (Iyer, 1990). When plasticization occurs by a mechanical process, the plasticizer must partition from the aqueous phase to the polymer phase and subsequently diffuse throughout the polymer. The rate and extent of this partitioning for an aqueous dispersion is dependent on the solubility of the plasticizer in water and its affinity toward the polymer phase. Bodmeier and Paeratakul (1994) found the equilibrium of plasticizer distribution in an aqueous dispersion of ethyl cellulose for water soluble plasticizers, such as TEC, occurred rapidly whereas the time needed to achieve equilibrium distribution for water insoluble plasticizing agents, such as TBC, required greater than 24 h. Gutierrez-Rocca (1993) also reported rapid partitioning of the water soluble plasticizers, TEC and triacetin, with Eudragit® L 30 D. Adsorption studies carried out to 72 h did not demonstrate any increase in the adsorption of these plasticizers to the polymers. Long equilibrium times of 36 h were reported for the insoluble plasticizers, TBC and acetyl tributyl citrate, to allow for the partitioning of the plasticizers into the acrylic polymer. If insufficient time is allowed for the plasticizer to partition into the polymer phase, the unincorporated plasticizer droplets, as well as the plasticized polymer particles, are sprayed on to the substrates during the coating process. Uneven plasticizer distribution within the film could result and potentially cause changes in the physical mechanical properties of the film during aging. To allow for the plasticizer to partition from the aqueous phase to the polymer phase, the TEC was mixed with the polymeric dispersion for at least 30 min. For the water insoluble TBC, mixing times were extended to 48 h to ensure that plasticization of the polymer had occurred.

The effects of the plasticizers and the two fill liquids on the disintegration times of SGC coated with Eudragit® L 30 D-55 in 0.1N HCl solution

Table 1
Initial disintegration times of SGC coated with Eudragit® L 30 D-55 in 0.1 N HCl

Fill liquid	%L 30 D	Plasticizer	Enteric protection
PEG 400	uncoated	none	3 min
PEG 400	5%	20% TEC	> 4 h
PEG 400	10%	20% TEC	> 4 h
PEG 400	15%	20% TEC	> 4 h
PEG 400	5%	20% TBC	0.5 h
PEG 400	10%	20% TBC	0.5 h
PEG 400	10%	10% TEC/ 10% TBC	> 4 h
PEG 400	10% + 2% HPMC	20% TEC	> 4 h
Miglyol®	uncoated	none	3 min
Miglyol®	10%	20% TEC	> 4 h
Miglyol®	10%	20% TBC	3 h
Miglyol®	10%	10% TEC/ 10% TBC	> 4 h
Miglyol®	10% + 2% HPMC	20% TEC	> 4 h

are listed in Table 1. Uncoated SGC ruptured and released the fill liquid within 3 min regardless of the fill liquid. Complete dissolution of the SGC occurred within 7 min in the acidic media. Protection from disintegration of the SGC was seen for both fill liquids when TEC was the plasticizing agent. The films containing the water insoluble plasticizer, TBC, did not provide enteric protection to capsules containing PEG 400, a hydrophilic fill liquid. However, film coatings containing the TBC alone in capsules containing the hydrophobic fill liquid, Miglyol®, showed much improved enteric protection. Film coatings containing the TBC in combination with TEC provided enteric protection for both Miglyol® and PEG containing capsules. Enteric protection was also achieved for capsules which received a 2% HPMC subcoat prior to the acrylic coating, regardless of the fill liquid.

Capsules were stored in open containers at room temperature and at either 0 or 96% relative humidity while capsules stored under ambient conditions were placed in glass containers with screw-top lids. Enteric protection was followed over a 3 month period. No change in enteric protection was noted in capsules that initially exhibited enteric protection for at least 4 h, with the exception of the lots that agglomerated and

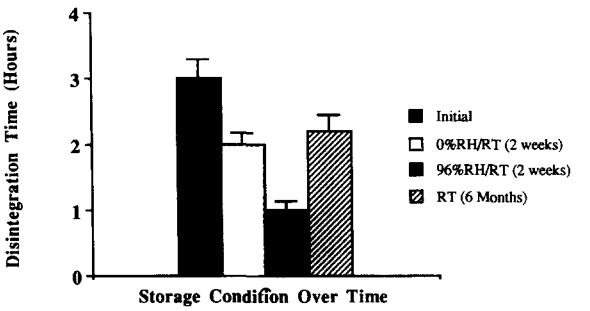

Fig. 1. Enteric protection of SGC containing Miglyol® coated with Eudragit® L 30 D-55 plasticized with TBC during storage.

were unable to be tested, as shown in Table 2. A 5% level of Eudragit® L 30 D-55 was not sufficient to protect the capsules containing PEG from agglomeration at 96% relative humidity and room temperature (96% RH/RT). At 10 and 15% coating levels, better protection from the environment was achieved. These findings are in agreement with those of Murthy and co-workers (1986, 1987) who reported a higher level of polymeric film was required to protect the HGC from agglomeration under conditions of high humidity.

Capsules containing the HPMC subcoat also agglomerated during storage at 96% RH/RT, regardless of fill liquid. Gutierrez-Rocca and

Table 2
Disintegration times of SGC coated with Eudragit® L30D-55 during storage as a function of relative humidity

%L 30D-55	% plasticizer	0% RH/RT		96% RH/RT	
		1 month	3 months	1 month	3 months
PEG					
5%	20% TEC	> 4 h	> 4 h	[a]	[a]
10%	20% TEC	> 4 h	> 4 h	> 4 h	> 4 h
15%	20% TEC	> 4 h	> 4 h	> 4 h	> 4 h
10%	10% TEC 10% TBC	> 4 h	> 4 h	> 4 h	> 4 h
10% and 2% HPMC	20% TEC	> 4 h	> 4 h	> 4 h	[a]
Miglyol®					
10%	20% TEC	> 4 h	> 4 h	> 4 h	[a]
10%	10% TEC/ 10% TBC	> 4 h	> 4 h	> 4 h	> 4 h
10% and 2% HPMC	20% TEC	> 4 h	> 4 h	[a]	[a]

[a] Capsules agglomerated – unable to be tested.

McGinity (1994) reported that the glass transition temperature (T_g) of the acrylic polymer decreased during storage at high humidity due to the adsorbed water acting as a plasticizer and breaking the intermolecular hydrogen bonds of the polymer which resulted in a stickier film coating. In the present study, the HPMC subcoat acted as a barrier to slow moisture penetration. More water remained in the acrylic film, resulting in a lowering of the T_g and causing the product to agglomerate. Without the HPMC subcoat, the Miglyol® capsules coated with the acrylic polymer containing TEC as the plasticizer also agglomerated at high humidity probably due to the hydrophobic properties of the fill liquid, causing more moisture to remain in the film and lower the T_g.

Enteric protection of Miglyol® containing capsules coated with Eudragit® L 30 D-55 with TBC as the plasticizer was found to decrease during storage, as shown in Fig. 1. Initially, the coated capsules could withstand 3 h in acidic media. After 2 weeks storage at 0% RH/RT, enteric protection decreased to 2 h while enteric protection decreased to 1 h in the capsules stored at 96% RH/RT. The disintegration times were also found to drop after 6 months storage under ambient conditions. This result could be due to the partitioning of the TBC from the film into the hydrophobic fill liquid. Schulze and McGinity (1993) found the Eudragit® L polymers were very brittle. With the migration of plasticizer from the film into the fill liquid, the film will become more brittle and crack, resulting in failure of the acrylic film. Further studies are needed to investigate this plasticizer migration more fully.

In agreement with the findings of Murthy and co-workers (1986) with hard gelatin capsules, no discernible difference in the enteric protection of the SGC was observed between capsules that had a protective subcoat of HPMC and those without a subcoat, regardless of the fill liquid, during storage at 0% relative humidity and room temperature (0% RH/RT). The HPMC subcoat was found to adhere to the gelatin shell wall initially, but adherence was impaired over time and separation of the film from the gelatin shell occurred during storage. With hard gelatin capsules, Thoma and Bechtold (1986) had reported improved adhesion of an enteric polymer to the shell of the HGC when a subcoat of HPMC was initially applied.

The moisture content of the soft gelatin capsules was investigated due to the potential effects that moisture may exert on the physical properties of the film and the gelatin shell. The coated capsules containing PEG initially possessed a significantly higher moisture content than those containing Miglyol®, as shown in Table 3. During storage at 0% RH/RT, the moisture content of the gelatin decreased in both Miglyol®- and PEG-containing SGC. Previous reports in the literature discuss the migration of water from the gelatin shell of HGC (Bond et al., 1970; Bell et al., 1973). The present study found that the moisture content increased during storage at 96% RH/RT, regardless of the fill liquid. However,

Table 3
Moisture content of SGC coated with Eudragit® L 30 D-55 during storage as a function of relative humidity

Storage	Fill	Plasticizer	Initial	1 month	2 months	3 months
0% RH/RT	PEG	TEC	4.96%	2.73%	1.81%	1.36%
	PEG	TEC/TBC	4.78%	2.56%	1.79%	1.12%
	Miglyol®	TEC	1.15%	0.00%	0.00%	0.00%
	Miglyol®	TEC/TBC	2.46%	0.00%	0.00%	0.00%
96% RH/RT	PEG	TEC	4.96%	6.58%	9.35%	9.18%
	PEG	TEC/TBC	4.78%	7.47%	9.03%	8.90%
	Miglyol®	TEC	1.15%	13.11%	11.21%	[a]
	Miglyol®	TEC/TBC	2.46%	13.62%	11.06%	11.60%

[a] Capsules agglomerated – unable to test.

the gelatin shell of the capsules containing Miglyol® gained more moisture than PEG capsules, probably due to the hydrophobic nature of the Miglyol®. Under high humidity, water migrated through the acrylic coating into the gelatin shell. The water continued to migrate into the hydrophilic PEG liquid, whereas the hydrophobic properties of the Miglyol® prevented water migration into the fill liquid. The water remained in the gelatin which resulted in an increased moisture content of the gelatin shell. This explanation is in agreement with Strickland and co-workers (1962) who found the direction of water transfer was determined by the relative hygroscopicity of the gelatin capsule and the fill contents and Serajuddin and co-workers (1986) who reported the extent of the migration of water into the fill material of the SGC depended on the nature of the solvent used in the fill liquid.

The moisture content of the gelatin shell affects the mechanical properties of the gelatin capsules. Kontny and Mulski (1989) related relative humidity to capsule brittleness and found that below forty percent relative humidity, HGC became brittle. Liebowitz and co-workers (1990) found increased brittleness occurred when HGC were exposed to high temperatures and low relative humidities. Because SGC contain a high level of moisture and a plasticizer which imparts characteristic flexibility to the gelatin, the moisture content was correlated to the physical strength of the coated SGC. Using an Instron universal testing apparatus, the load strength of the coated capsules was measured. During storage at 0% RH/RT, the strength of the capsules was expected to decrease, as the moisture content of the capsules decreased. Shah and co-workers (1992) had found SGC containing PEG 400 as the fill material became brittle upon aging and explained the result as possibly due to water and plasticizer migration from the shell into the fill liquid. In this study, however, the strength of the PEG capsules coated with Eudragit® L 30 D-55 and stored at 0% RH/RT was found to increase as the moisture levels of the gelatin shell decreased (Fig. 2). The load strength of the Miglyol® capsules also increased over the three month period, as shown in Fig. 3, although the moisture

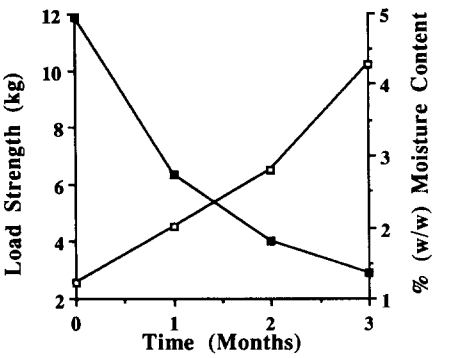

Fig. 2. Comparison of load strength and moisture content of coated SGC containing PEG (moisture content, $n = 4$; load strength, $n = 3$): moisture content (■); load strength (□).

content of the gelatin shell remained constant after the first month. Capsules coated with Eudragit® L 30 D-55 containing the TEC plasticizer exhibited this phenomenon as well as the capsules coated with films containing the TEC/TBC combination. One possible explanation for this surprising result could be due to the migration of the plasticizer from the acrylic film into the gelatin shell thus making the shell more flexible and able to withstand higher pressures.

In conclusion, a method for the application of an aqueous dispersion of an acrylic polymer to soft gelatin capsules was developed. The results of this study demonstrated that the film coating of SGC with Eudragit® L 30 D-55 plasticized with TEC provided good enteric protection, re-

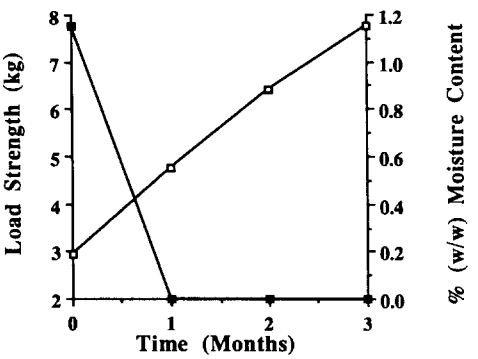

Fig. 3. Comparison of load strength and moisture content of coated SGC containing Miglyol® (moisture content, $n = 4$; load strength, $n = 3$): moisture content (■); load strength (□).

gardless of the fill liquid. The properties of the fill liquid, however, in conjunction with the hydrophobic plasticizer TBC, were found to influence the degree of enteric protection. Changes in the enteric protection of the Miglyol® capsules coated with Eudragit L 30 D-55 containing TBC as the plasticizing agent occurred during storage, possibly due to plasticizer migration from the acrylic film into the gelatin, resulting in an increased brittleness in the films and ultimately crack formation and film failure. An increase in load strength of the gelatin shell was noted in all formulations, possibly attributed to the migration of the plasticizer into the gelatin. While this initial study suggests possible migration of the plasticizer from the acrylic films into the gelatin shell, further studies are in progress to investigate the kinetics of plasticizer diffusion.

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