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International Journal of Pharmaceutics 202 (2000) 63–70

international journal of pharmaceutics

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Influence of Vitamin E TPGS on the properties of hydrophilic films produced by hot-melt extrusion

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Received 21 December 1999; received in revised form 27 March 2000; accepted 27 March 2000

Abstract

Films containing hydroxypropylcellulose (HPC) and polyethylene oxide (PEO) were prepared using a Randcastle extruder (Model 750) with and without Vitamin E TPGS (TPGS, D-α-tocopheryl polyethylene glycol 1000 succinate) as an additive. Conventional plasticizers including polyethylene glycol 400 (PEG 400), triethyl citrate (TEC), and acetyltributyl citrate (ATBC) were also incorporated into films containing a 50:50 blend of HPC and PEO. The physical–mechanical properties including tensile strength (TS) and percent elongation (%E) were determined on an Instron according to the ASTM standards. Glass transition temperatures (T_g) of the extruded films were determined utilizing a DSC 2920 Modulated differential scanning calorimeter and THERMAL ANALYST 2000 software. Gel permeation chromatography was used to study the stability of the polymer films under the processing conditions. The addition of 1, 3, and 5% Vitamin E TPGS, respectively, decreased the glass transition temperature of the extruded films containing either a 50:50 or 80:20 ratio of HPC to PEO in an almost linear fashion. In addition, the presence of 3% Vitamin E TPGS lowered the T_g over 11°C when compared with the HPC/PEO 50:50 blend film without TPGS, thus functioning as a plasticizer. The tensile strength decreased with increasing concentrations of TPGS, and the %E increased over 3-fold when compared with the HPC/PEO film that contained no additives. The film containing 3% Vitamin E TPGS had a similar tensile strength to that of the films containing 3% PEG 400, and a 3-fold increase in percent elongation when compared with the films containing 3% TEC and 3% ATBC. In addition, the Vitamin E TPGS facilitated the processing of the HPC/PEO films by decreasing the barrel pressure, drive amps, and torque of the extruder equipment.

Keywords: Vitamin E TPGS; Hot melt; Extruded films; Hydroxypropylcellulose; Physical–mechanical properties; Glass transition temperature; Polyethylene oxide

1. Introduction

Vitamin E TPGS NF (TPGS, D-α-tocopheryl polyethylene glycol 1000 succinate) has been utilized for numerous applications in pharmaceutical dosage forms. Its chemical structure contains both

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0378-5173/00/$ - see front matter
PII: S0378-5173(00)00418-X

a lipophilic and a hydrophilic moiety, making it similar to a conventional surface-active agent (Fig. 1). The chemical properties of this distinctive compound have suggested its use as a solubilizer, an emulsifier, an absorption enhancer, and as a water-soluble source of vitamin E (Eastman Chemical Company, 1998). TPGS has a melting point of approximately 38°C and its degradation temperature has been reported to be 199.3°C. These physical properties coupled with its chemical properties make TPGS a potential candidate for hot-melt extrusion applications.

Several studies have demonstrated the effects of TPGS as an absorption enhancer (Traber et al., 1986, 1987; Sokol et al., 1991a,b; Argao et al., 1992; Sokol et al., 1993; Chang et al., 1996; Bridgers et al., 1998). Sokol et al. (1993) conducted a multi-center trial of TPGS for treatment of vitamin E deficiency in children with chronic cholestasis . These researchers reported that TPGS appeared to be a safe and effective form of vitamin E for reversing or preventing vitamin E deficiency during chronic childhood cholestasis. Traber et al. (1986) proposed a mechanism for enhanced α-tocopherol absorption by TPGS. Since TPGS can form micelles, it can cross from the intestinal lumen into the intestinal cells. This mechanism has suggested the use of TPGS as a controlled drug delivery vehicle. Other studies have demonstrated an enhanced absorption of vitamin D in chronic cholestatic liver disease of infancy and childhood (Argao et al., 1992) and improved absorption of a model HIV protease inhibitor (Bridgers et al., 1998). Ismailos et al. (1994) concluded that TPGS increased the solubility of cyclosporine, resulting in an increased bioavailability and thus an increased absorption.

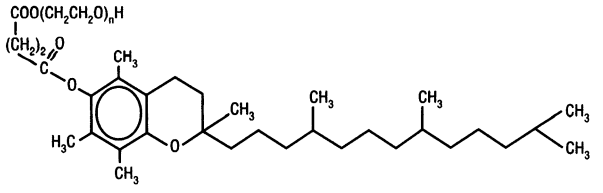

Fig. 1. Chemical structure of the principal component of Vitamin E TPGS.

Several studies have also demonstrated the value of TPGS as a water-soluble vitamin E supplement (Hidiroglou et al., 1993; Traber et al., 1994; Dimitrov et al., 1996; Socha et al., 1997). Socha et al. (1997) concluded that oral TPGS supplementation of cholestatic children can quickly normalize serum vitamin E levels. Dimitrov et al. (1996) reported that in cases of cholestasis and other forms of lipid malabsorption, oral administration of TPGS is the treatment of choice.

Few, if any, studies have been reported in the literature concerning the physical–mechanical properties of Vitamin E TPGS in hydrophilic films produced by a hot-melt extrusion technique. Due to the unique properties of TPGS as a solubilizer, absorption enhancer and a potential controlled drug release vehicle, transdermal and transmucosal applications are also possible. The objective of this study is to investigate the influence of Vitamin E TPGS on the properties of hydrophilic films produced by a hot-melt extrusion technique. In addition, the effect of TPGS as a processing aid for hot-melt extrusion is reported.

2. Materials and methods

2.1. Materials

Vitamin E TPGS NF was provided by Eastman Chemical Company (Kingsport, TN). Hydroxypropylcellulose (HPC) (Klucel® HF; molecular weight (MW), 1 150 000) was obtained from the Aqualon Company (Wilmington, DE). Polyethylene oxide resin (PEO) (PolyOx® WSR; MW, 1 000 000) and polyethylene glycol 400 NF (PEG 400) (Carbowax® 400) were obtained from Union Carbide Corp. (Danbury, CT). Triethyl citrate (TEC) and acetyltributyl citrate (ATBC) were provided by Morflex, Inc. (Greensboro, NC).

2.2. Processing methods

2.2.1. Material preparation and blending

HPC and PEO were dried at 50°C for 24 h prior to mixing. Vitamin E TPGS was freeze-dried, lyophilized, and sieved (60 mesh) prior to

blending with the two ratios of HPC and PEO (50:50 and 80:20). The plasticizers were incorporated slowly into a Liquid–Solids Blender® (Paterson-Kelley Co.) containing the HPC/PEO blends. All additives were blended for 30 min. The batch size was 1.0 kg.

2.2.2. Hot-melt extrusion

A Randcastle Microtruder® (Model RCP-0750) was pre-heated to 170°C melt temperature. For purging purposes, polyethylene pellets were added to the hopper and passed through the extruder for 5 min (this procedure was repeated for each individual batch). The blends of HPC/PEO and Vitamin E TPGS or plasticizer was placed in the hopper and extruded to obtain a homogeneous film with a thickness range from 10 to 13 mil (1 mil = 25.4 μm or 0.001 inch) or 0.254–0.330 mm. The extrusion temperatures for each film were dependent on the formulation extruded. The films were extruded at their respective optimal temperatures, ranging from 180 to 190°C. Processing time was less than 2 min for all films produced. The film was collected in rolls, labeled, and sealed in 5 mil polyethylene bags (25°C, 50% relative humidity). The width of the films produced was approximately 5.00 inches (± 0.25). Random samples were taken from the extruded films for testing. Initial testing was commenced after 7 days of storage.

2.3. Mechanical testing apparatus

The physical–mechanical properties of the films were distinguished utilizing an Instron 4201 testing apparatus with a head speed of 10 mm/min. The standard test method for tensile properties of thin plastic sheeting by the American Society for Testing Materials, method D 882-95a, was used to investigate the mechanical properties. Six samples from each formulation were tested. The initial grip separation was 100 mm. Testing conditions for all films were 25°C and 50% relative humidity.

2.4. Calculations

Calculations were performed in the following manner.

$$\text{Tensile strength } (\sigma) = \frac{\text{force or load } (F)}{\text{MA}}$$

where F is the maximum load and MA is the minimum cross-sectional area of the film specimen. Results were converted to megaPascal units (MPa).

$$\text{Strain } (\varepsilon) = \frac{L_o - L}{L_o} = \frac{\Delta L}{L_o}$$

where L_o refers to the initial length of the film sample and L is the elongation at the moment of rupture.

$$\text{Elongation percent} = \varepsilon \times 100$$

2.5. Physical characterization

Differential scanning calorimetry (DSC 2920 Modulated DSC, and THERMAL ANALYST 2000 software; TA Instruments, New Castle, DE) was utilized to determine glass transition temperatures (T_g). Ultrahigh pure nitrogen was used as the purge gas at a flow rate of 150 ml/min. Approximately 5–10 mg of sample was weighed and sealed in a nonhermetic aluminum pan. All studies had a temperature ramp speed set at 10°C/min.

Gel permeation chromatography (GPC) was used to provide a qualitative study of the polymer blend stability. A Waters system, including a WISP model 710B auto sampler and a model 510 solvent delivery system, was utilized. Ultrahydrogel® 1000 and 2000 columns connected in series and a model 410 differential refractometer were used as the detector. Distilled water containing 0.1 M sodium nitrate was utilized as the mobile phase at a flow rate of 1 ml/min.

2.6. Statistical analysis

Statistical analysis was determined utilizing one-way analysis of variance. A statistically significant difference was considered when $P < 0.05$.

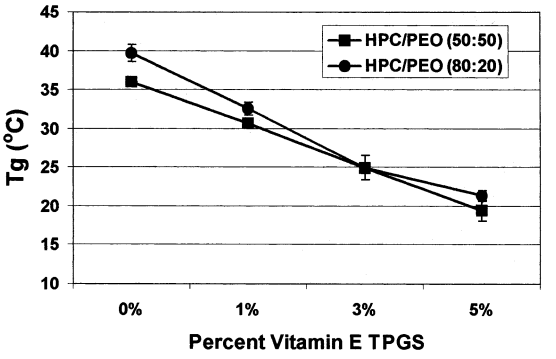

Fig. 2. Glass transition temperatures of films containing different levels of Vitamin E TPGS incorporated into two formulations of HPC/PEO hot-melt extruded films ($n = 4$).

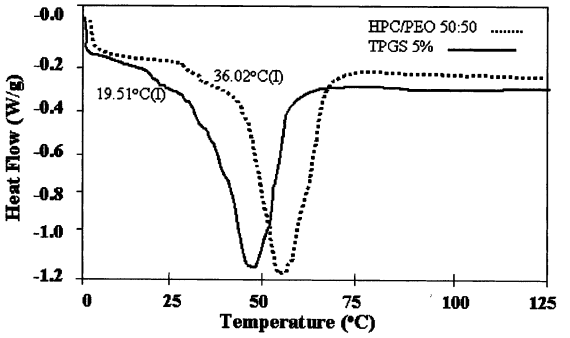

Fig. 3. Differential scanning calorimetry thermograms of hot-melt extruded films consisting of HPC/PEO in a 50:50 ratio (dashed line) and the HPC/PEO 50:50 ratio with 5% Vitamin E TPGS as an additive (solid line).

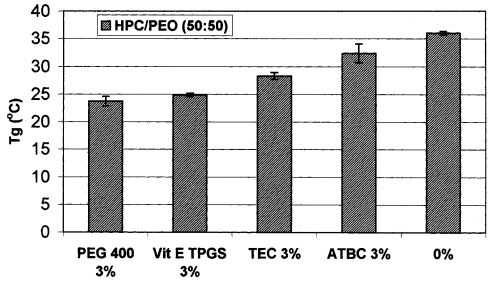

Fig. 4. Glass transition temperatures of HPC/PEO (50:50) hot-melt extruded films containing Vitamin E TPGS and three conventional plasticizers ($n = 4$).

3. Results and discussion

As seen from Fig. 2, the glass transition temperatures of the two formulation ratios of HPC and PEO decreased in an almost linear fashion with the addition of 1, 3 and 5% Vitamin E TPGS. Although the T_g of the HPC/PEO (80:20) film with no TPGS present was slightly higher than that of the 50:50 ratio, with the addition of only 1% TPGS, the T_g of the two films were almost equivalent. In addition, the incorporation of 5% TPGS into the HPC/PEO films (50:50 and 80:20) lowered the glass transition temperatures by approximately 17 and 18°C, respectively (36.0 to 19.5°C, and 39.7 to 21.3°C), compared with the HPC/PEO films with no additives ($P < 0.05$) (Fig. 3). By lowering the glass transition temperature, TPGS acts as a plasticizer for the two polymer-blended films. These effects are a result of the TPGS weakening the intermolecular attractions within the polymer blends and increasing the polymers' free volume, allowing the polymer chains to move more easily and to become more flexible (Gutierrez-Rocca and McGinity, 1993; Wheatley, and Steuernagel, 1997).

The T_g of the HPC/PEO (50:50 ratio) film containing 3% TPGS and three other conventional plasticizers at the same concentration was determined (Fig. 4). The film containing TPGS (3%) lowered the glass transition temperature over 11°C from the HPC/PEO, 50:50 blend film (36.0 to 24.9°C). In addition, the 3% TPGS-incorporated film reduced the T_g to the same degree as the 3% PEG 400, and was significantly better than films containing 3% TEC and 3% ATBC ($P < 0.05$). The efficiency of a plasticizer is related to its chemical structure and the interaction between its functional groups with those of the polymer or polymers (Gutierrez-Rocca and McGinity, 1994). The ampiphilic nature of the TPGS molecule, with the polyethylene glycol moiety serving as the polar head, enables it to function as a plasticizer for the two hydrophilic polymers (Eastman Chemical Company, 1998).

Fig. 5a,b show the tensile strength and percent elongation, respectively, of the two HPC/PEO polymer blends as a function of increasing percentages of Vitamin E TPGS. The tensile strength (TS) is indirectly proportional to the percentage

of TPGS, while the percent elongation (%E) is directly proportional. No differences in these two physical–mechanical properties were found for the two HPC/PEO blends. This finding is not surprising since there were no significant differences in the glass transition temperatures between the two polymer blends at each level of TPGS incorporated. The percent elongation increased over 3-fold for the 5% TPGS-containing film when compared with films containing no TPGS ($P < 0.05$). These findings are also consistent with the T_g data that were presented earlier. Plasticization of a polymer will decrease the polymeric intermolecular interactions to provide a greater freedom of movement for the polymeric molecules. Therefore, the film is more deformable (Wang et al., 1996). The tensile strength is decreased, and flexibility and elongation is increased, as is reported in this study.

The physical–mechanical studies demonstrate the comparable effectiveness of Vitamin E TPGS as a plasticizer (Fig. 6a,b). The 3% TPGS-incorporated film had a similar tensile strength to that of the 3% PEG 400-containing film (17.9 compared with 14.8 MPa). However, the TS of the TPGS-containing film was significantly lower than the films incorporated with 3% TEC, 3% ATBC and the HPC/PEO film (50:50 blend) containing no additives. The 3% TPGS film also exhibited an almost 3-fold increase in percent elongation (14.9%) when compared with that of the TEC, ATBC, and 0% TPGS-containing films (6.4, 5.8 and 4.7%, respectively). Thus, the hydrophilic moiety of the Vitamin E TPGS molecule was more effective in disrupting the intermolecular interactions of the HPC/PEO 50:50 film, allowing a greater degree of polymer chain freedom than either TEC or ATBC. Only the 3% PEG 400-incorporated film had a greater percent elongation (21.3%) than the TPGS film. This may be explained by the lower molecular weight of PEG compared with the TPGS. Heinamaki et al. (1994) presented similar findings. These researchers

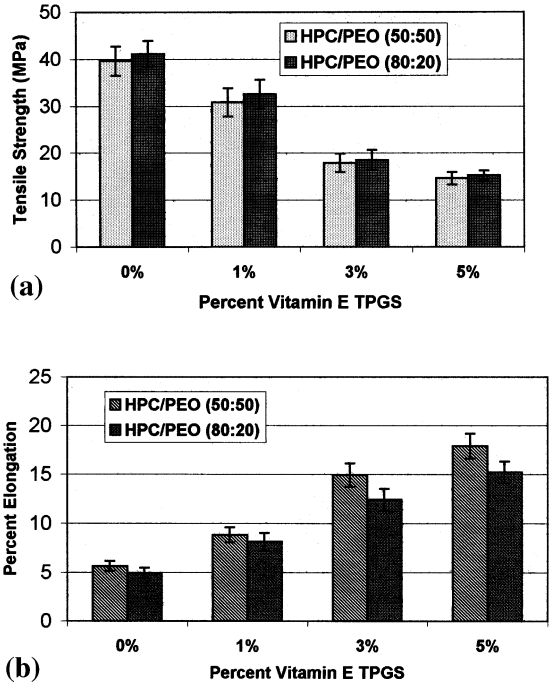

Fig. 5. (a) Tensile strength and (b) percent elongation of different levels of Vitamin E TPGS incorporated into two formulations of HPC/PEO hot-melt extruded films ($n = 6$).

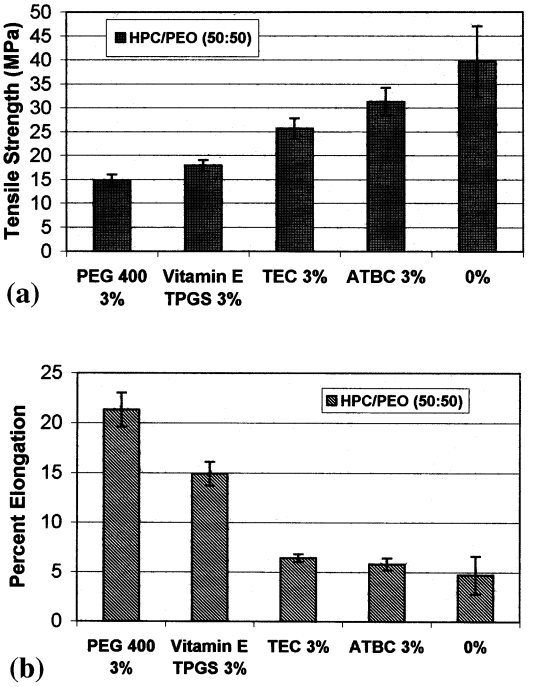

Fig. 6. (a) Tensile strength and (b) percent elongation of HPC/PEO 50:50 ratio hot-melt extruded films containing Vitamin E TPGS and three conventional plasticizers ($n = 6$).

found that percent elongation or ductility was primarily attributed to the molecular weight of the polymeric plasticizer. As the molecular weight or size of the PEG (or PEG moiety) is increased, the mole fraction of available hydroxyl groups to interact with the reactive sites of molecules will decrease (Rowe, 1976). In this case, the PEG moiety is of higher molecular weight than the PEG 400 molecule, therefore decreasing the ability of TPGS to interact with the reactive hydroxyl groups of the HPC and PEO. Thus, the TPGS film would be less elastic. In addition, PEG is composed of the same structural unit as PEO, but has a much lower molecular weight than PEO. Since PEG and PEO have the same repeating unit, they were completely miscible in the solid state (Zhang and McGinity, 1999). The PEG molecules between PEO chains were able to more effectively weaken the cohesive interactions between the PEO chains, thereby increasing the inter-chain space between the PEO molecules. However, as was reported by Repka et al., 1999, the PEG 400-containing films may have stability concerns upon aging.

The influence of Vitamin E TPGS on processing conditions of hot-melt extruded films is reported in Table 1. In a hot-melt extrusion process, polymers are subjected to both thermal and shearing stresses. The temperature can contribute to depolymerization of polymer chains, whereas chain scission may result from the shearing effects of the screw (Zhang and McGinity, 1999). In the absence of TPGS, films could not be processed at 180°C due to the high viscosity of the polymer blend and a torque that exceeded the capacity of the extruder (50 N m). The processing temperature had to be increased to a minimum of 190°C to obtain a HPC/PEO 50:50 ratio film. Increasing the temperature is the most common practice to facilitate a polymer extrusion process in the plastic industry. Melt viscosity decreases exponentially with respect to an increase in temperature (Nielsen, 1977). At 180°C, a film with as little as 1% TPGS could be produced. However, as the percent TPGS increased, the barrel pressure, drive amps, and torque all decreased significantly ($P < 0.05$). Thus, in addition to TPGS plasticizing the HPC/PEO films, it was also an excellent processing aid in the extrusion process. Indeed, due to the decrease in melt viscosity with increasing TPGS concentration, the films incorporated with TPGS could be produced at a lower temperature and/or a higher screw speed. This would decrease the potential for degradation of both the polymers and drugs that may be incorporated in the film.

Fig. 7 shows the results from the GPC studies. As one can observe, there is a shift to the left of the curve representing the film containing 3% TPGS compared with that of the curve of the HPC/PEO 50:50 ratio film with no additives. These findings demonstrated that TPGS decreased the degradation and chain scission of the polymer blend and help stabilize the PEO that is susceptible to thermal oxidation. In addition, when Vitamin E 0.5% was added to the powder blend, there was no further shift than occurred with the 3% TPGS-incorporated film.

Vitamin E TPGS is a viable candidate for incorporation into hot-melt extruded films composed of HPC and PEO. TPGS functioned as a plasticizer for these hydrophilic films since it lowered the glass transition temperature and increased the percent elongation as the TPGS

Table 1
Processing conditions for hot-melt extruded films containing a 50:50 ratio of hydroxypropylcellulose to polyethylene oxide with Vitamin E TPGS as an additive ($n = 4$)

Vitamin E TPGS (%)	Melt temperature (°C)	Pressure (psi)	Drive (A)	Torque (N·m)	Screw speed
0	180	>3000	>4.00	Overload	25
0	190	2100	3.84	40	40
1	180	1800	3.06	33	40
3	180	1500	2.61	28	40
5	180	1100	2.07	21	40

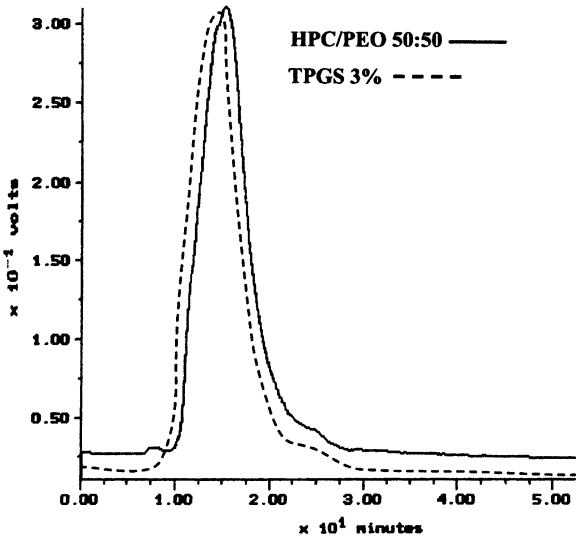

Fig. 7. Gel permeation chromatograms of hot-melt extruded films consisting of HPC/PEO in a 50:50 ratio and the HPC/PEO 50:50 ratio with 5% Vitamin E TPGS as an additive ($n = 6$).

content increased. TPGS was also found to function comparably with the conventional plasticizers tested. Vitamin E TPGS was also an excellent processing aid, decreasing barrel pressure, drive amps, and torque as the TPGS percent increased. TPGS may also act to prevent polymer degradation when utilized in the extrusion process. In summary, the unique properties of Vitamin E TPGS can function to promote more applications and opportunities in wound care and in transdermal/transmucosal drug delivery.

Acknowledgements

Michael A. Repka would like to thank the American Foundation for Pharmaceutical Education for its support of this study and other research endeavors.

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