Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion

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Abstract

The thermal stability of polyethylene oxide (PEO) in sustained release tablets prepared by hot-melt extrusion was investigated. The weight average molecular weight of the polymer was studied using gel permeation chromatography. The chemical stability of PEO was found to be dependent on both the storage and processing temperature, and the molecular weight of the polymer. Storage of the polymer above its melting point significantly increased polymer degradation, and the degradation process was accelerated as the molecular weight was reduced. The thermal stability of PEO $M_W=1,000,000$ (PEO 1M) in sustained release chlorpheniramine maleate (CPM) tablets prepared by hot-melt extrusion was found to depend on the processing temperature and screw speed. Lower molecular weight PEO $M_W=100,000$ (PEO 100K) was demonstrated to be a suitable processing aid for PEO 1M. Incorporation of PEO 100K reduced degradation of PEO 1M and did not alter the release rate of CPM. Vitamin E, Vitamin E Succinate and Vitamin E TPGS were found to be suitable stabilizers for PEO, however, ascorbic acid was shown to degrade the polymer in solution. Thermal analysis demonstrated that Vitamin E Succinate and Vitamin E TPGS were dispersed at the molecular level in hot-melt extruded tablets. Solubilized Vitamin E Succinate and Vitamin E TPGS suppressed the melting point of the polyethylene oxide. Drug release rates from hot-melt extruded tablets stabilized with antioxidants were found to be dependent on the hydrophilic nature of the antioxidant. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Hot-melt extrusion; Extruded tablets; Polyethylene oxide; Stability; Antioxidants; Chlorpheniramine maleate

1. Introduction

Hydrophilic polymers have been used extensively to prepare sustained and modified release drug delivery systems. Several research groups have demonstrated the hot-melt extrusion technique [1] to be a viable method to prepare pharmaceutical dosage forms including granules [2], pellets [3], sustained release tablets [4,5] and transdermal drug delivery systems [6–8].

Dosage forms produced by the hot-melt extrusion method require a pharmaceutical grade thermoplastic material. Polyethylene oxide (PEO) is a free flowing, thermoplastic homopolymer synthetized by the heterogeneous catalytic polymerization of ethylene oxide monomer. It is commercially available in a wide range of molecular weights ($100,000–8,000,000$). PEO is miscible with water in all ratios due to hydration of the ether oxygen. PEO is a semi-crystalline polymer with a melting range of 57–73°C.

PEO has been widely used to prepare sustained release dosage forms. Studies have shown that the high molecular weight PEO successfully delayed the release rate of soluble and insoluble drugs from matrix tablets prepared by direct compression [9,10]. Apicella and coworkers [11] used PEO to produce buccal adhesive etofylline films by solvent casting methods. Stringer and Peppas [12] prepared cross-linked PEO hydrogels using gamma irradiation. Efentakis and Vlachou [13] incorporated PEO as the rate-controlling carrier in sustained release gelatin capsules with both soluble and insoluble model drugs. Zhang and McGinity [4] investigated the drug release properties of sustained release tablets prepared by hot-melt extrusion techniques.

Few studies have been reported in the literature concerning the stability of polymers in sustained release matrix tablets prepared by hot-melt extrusion. During
hot-melt extrusion, polymers are subject to mechanical, thermal and oxidative degradation. Mechanical degradation may be induced by the shear effects imposed by the rotating screw. Thermal depolymerization results from high temperatures and includes random scission, scission from the ends of the polymer and unzipping of substitute groups. Oxidative degradation is the result of a chemical reaction between oxygen molecules and the polymer.

The objectives of the present study were to investigate the thermal stability of PEO (MW = 1,000,000 or PEO 1M) in sustained release chlorpheniramine maleate (CPM) tablets prepared by the hot-melt extrusion process. The influence of processing conditions on polymer stability was studied. Low molecular weight PEO (MW = 100,000 or PEO 100K) was incorporated as a plasticizer to facilitate processing and antioxidants were included to stabilize the polymer. The influence of processing parameters and incorporation of a plasticizer and antioxidants on the drug release properties of the tablet was also investigated. Furthermore, the chemical stability of PEO under accelerated storage conditions (40°C, 60°C and 80°C all at 75% relative humidity) was determined.

2. Materials and methods

2.1. Materials

PEO resins were purchased from Union Carbide Corp. (Danbury, CT) and Polysciences, Incorporated (Warrington, PA). Vitamin E, Vitamin E acetate, Vitamin E Succinate, ascorbic acid, butylated hydroxyanisole, sodium perchlorate, triethylamine and CPM were purchased from Spectrum Chemical Co. (Gardena, CA). Vitamin E TPGS (D-α tocopheryl polyethylene glycol 1000 succinate) was supplied by Eastman Fine Chemicals (Kingsport, TN). Methanol was purchased from EM Science (Gibbstown, NJ). All materials were passed through a 20 mesh screen prior to use.

2.2. Thermogravimetric analysis

Thermogravimetric analysis (TGA) was used to determine the thermal degradation temperature of the polymer. A Perkin-Elmer (Norwalk, CT) 7-series Thermogravimetric analyzer was used in this study. Samples weighing approximately 20 mg were used for the analysis. Nitrogen of ultrahigh purity was used as the purging gas for the furnace chamber. The temperature ramp speed was set at 20°C/min, and the percentage weight loss of the samples was monitored from 30°C to 900°C.

2.3. Molecular weight determination

Gel permeation chromatography was used to study the stability of the polymer by measuring its weight average molecular weight. All standards and samples were prepared at 0.5% w/w concentrations in mobile phase under gentle agitation on a radial shaker (Aberbach Corp., Ann Arbor, MI) for 12 h and injected immediately. A Waters analytical system was used that included a WISP model 710B auto sampler (100 μl sample injection volume), model 510 pump, Ultrahydrogel® Columns (2000 and 1000 in series) and a model 410 differential refractometer as the detector. The data were collected using Millennium® Version 3.2 software. A third order calibration curve (R² ≥ 0.99) was built using PEO standards (Polymer Standards Service, Silver Spring, MD) with peak molecular weights ranging from 4450 to 1,700,000. The mobile phase was double-distilled water containing 0.1 M sodium nitrate and was pumped at a flow rate of 0.8 ml/min. The columns were held at an operating temperature of 35°C during analysis. Injection precision was found to have a relative standard deviation (RSD) of 1.5% for 10 injections.

2.4. Differential scanning calorimetry analysis

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of the polymer, drug and antioxidants in physical mixtures and hot melt extrudates. The DSC instrument was a model 2920 from TA Instruments (New Castle, DE). Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 150 ml/min. Approximately 10 mg of sample was weighed and sealed in aluminum pans. The temperature ramp speed was 5°C/min from 25°C to 150°C for all studies.

2.5. Hot-melt extrusion process

Prior to each run, the system was purged with polyethylene for 10 min followed by a 15 min purge of PEO. The drug, polymer(s) and or antioxidants were geometrically diluted and introduced into a Robot Coupe High Shear Blender (Model RS1 3VG, Jackson, MS) and mixed at 2000 rpm for 3 min. The resultant blend was fed into a single-screw Randcastle Extruder (Model RC 0750, Cedar Grove, NJ) equipped with a Nitralloy 135M screw (3:1 compression ratio with flight configuration containing feed, compression and mixing sections) and a rod shaped die (6 mm in diameter). The screw speed was either 10, 20, 40 or 60 rpm. The three heating zones and die temperatures were set and allowed to equilibrate. The residence time of the materials in the extruder was approximately 2–3 min. The extrudates were cooled to 45–55°C and manually cut into tablets weighing 250 mg.
2.6. In vitro release properties

Dissolution testing was performed according to apparatus II of USP 24 on a Van Kel VK7000 Dissolution Tester (Van Kel Industries, Edison, NJ 08820) equipped with an auto sampler (Model VK 8000). The dissolution medium (900 ml of purified water) was maintained at 37°C (Model 750D) and agitated at 100 rpm. Samples (5 ml) were removed at specified time points over a 12 h period.

Samples were analyzed for CPM content using a Waters (Milford, MA) high performance liquid chromatography (HPLC) system with a photodiode array detector (Model 996) extracting at 261 nm. Samples were pre-filtered through a 0.45 μm membrane (Gelman Laboratory, GHP Acrodisc). A WISP® auto sampler (Model 710B) was used to inject 20 μl samples. The data were collected and integrated using Millennium® Version 3.2 software. The column was a Waters μBondapak® C18 125Å (10 μm). 3.9 × 300 mm². The mobile phase contained a mixture of methanol:water:triethylamine in volume ratios of 675:325:2. The aqueous phase contained 0.71% w/w sodium perchlorate. The solvents were vacuum filtered through a 0.45 μm nylon membrane and degassed by sonication. The flow rate was 1.0 ml/min. The retention time of the CPM was 9 min. Linearity was demonstrated from 2 to 80 μg/ml ($R^2 > 0.997$) and injection repeatability was 0.38% RSD for 10 injections.

3. Results and discussion

3.1. Thermal stability of PEO

The incorporation of oxygen into the backbone of an aliphatic chain polymer results in thermal instability since the C–O bond is less stable than a C–C bond [14]. When exposed to air or oxygen, PEO has been reported to oxidatively degrade in both bulk [15] and in solution [16]. This degradation has been reported to accelerate at elevated temperatures. PEO is a semicrystalline polymer, essentially a two phase material consisting of spherulitic crystals embedded in an amorphous continuum. Maclaine and coworkers [17] reported the crystallinity of PEO of molecular weight 1,000,000 to be in the range of 45–55% using dilatometry. Oxygen permeability of a polymer in the solid state increases with polymer chain mobility. Due to the highly ordered structure of the crystalline spherulites, the oxygen diffusion rate is significantly lower in the crystalline region than in the amorphous region [18].

When PEO was stored below its melting point (range 55–80°C) at 40°C, or at 60°C, only the amorphous region and molten crystalline portions of the polymer are susceptible to oxidative degradation. When stored above its melting temperature at 80°C, both the crystalline and amorphous regions of the polymer are completely molten and the oxidative degradation of PEO was substantially accelerated. As polymer degradation accelerated, the physical appearance of the polymer changed, and when stored at 80°C for 14 days, PEO was soft and waxy with a distinctive odor.

The thermal oxidation of PEO was highly dependent on polymer molecular weight. The profiles in Fig. 2 demonstrate that the lower molecular weight polymer degraded more rapidly than the higher molecular weight polymer (100,000 > 600,000 > 1,000,000). Maclaine and coworkers [17] reported the crystallinity of PEO reached a maximum at molecular weight 6000 and decreased with increasing molecular weight. Because they are more crystalline, it was expected that low molecular weight polymer would be more resistant to thermal oxidation.

The melting point of a polymer crystal depends on its thickness, with smaller crystals melting at lower temperatures than larger crystals. Polymers are rarely crystallized to a uniform size and thus exhibit a melting range rather than a sharp melting point. The
manufacturing process can also influence crystal size if the cooling rate and time are not tightly controlled.

Ozeki and coworkers [18] observed that the onset of melting and the melting point of PEO increased as the molecular weight increased. These results were confirmed in the present study. The DSC scan of PEO (1M) in Fig. 3 reveals a melting range from 55°C to 80°C. When stored at 60°C, smaller crystals that melt below 60°C are more susceptible to oxidative degradation. Thus, it can be concluded from this study that a higher proportion of small crystals are present in the lower molecular weight PEO.

3.2. Hot-melt extrusion stability of PEO

The stability of PEO following hot-melt extrusion was investigated using a model formulation containing 20% CPM and 80% PEO 1M. The influence of hot-melt processing on the weight average molecular weight of three different lots of PEO 1M was investigated. When extruded at 20 rpm and 70–105°C, the reduction in weight average molecular weight ranged from 8.2% to 11.3% for the three lots. The differences from one lot to another were not statistically significant (n = 6, α = 0.05, p > 0.10).
The influence of extrusion conditions on the weight average molecular weight of PEO is presented in Fig. 4. At low screw speeds, polymer degradation increased with higher processing temperatures. These results suggest that thermal degradation rather than mechanical degradation was the dominant mechanism. Processing temperature and the transit time through the extruder were the parameters that significantly influenced the extent of PEO degradation. As screw speed was increased, polymer degradation decreased until melt fracture began to occur. The melt behavior of PEO has been reported to be pseudoplastic in nature \[19\]. As the screw speed increased, the melt viscosity decreased due to shear thinning and the transit time through the extruder decreased. Melt fracture will occur when the polymer chains are forced to orient themselves in the die and recoil into a random configuration upon exit. At very high screw speeds, polymer degradation was due to both mechanical and thermal degradation.

Melt fracture was observed at the zone temperatures of 80°C, 90°C, 110°C, 120°C and screw speed of 60 rpm, and at zone temperatures of 85°C, 100°C, 120°C, 140°C and a screw speed of 80 rpm. Melt fracture was not observed at the lower temperature settings due to drive overload. These findings demonstrate that polymer stability can be modulated by process parameters and that high material throughput can be achieved.

Most extruders are supplied with an ammeter which indicates the load or current supplied by the drive motor to the screw in order to move the polymer through the extruder. The influence of processing temperatures and screw speed on drive amperage is presented in Fig. 5. The drive amperage follows the same trends as polymer degradation at all three processing temperatures. At the processing conditions in which the polymer is more stable, the melt viscosity remained relatively high which created more resistance against the drive. As the polymer degrades, lower molecular weight chains are formed, melt viscosity is reduced and the drive amperage decreases. These findings demonstrate that drive amperage can be used as an indicator of polymer stability until melt fracture occurs. At the point of melt fracture, drive amperage decreased due to increased chain scission, in addition to relaxation and uncoiling of the polymer at the die exit.

### 3.3. Influence of low molecular weight PEO

Low molecular weight PEO (\(M_W=100,000\)) was investigated as a processing aid for the model formulation containing PEO 1M and CPM. The presence of PEO 100K reduced the melt viscosity, friction and chain entanglements between the PEO 1M molecules. As shown in Table 1, as the percentage of PEO 100K in the powder blend increased, the drive amperage decreased and the stability of PEO 1M increased.

In formulations A and B, the two different PEO polymers eluted as a single peak. However, formulation C, containing equal parts PEO 1M and PEO 100K eluted as two separate peaks. In this formulation, the weight average molecular weight of the PEO 100K polymer increased following extrusion. This demonstrates that degradation of PEO 1M during the

### Table 1

Extrusion stability of PEO 1M and the influence of PEO 100K on PEO weight average molecular weight as measured by gel permeation chromatography, \(\pm SD, n=3\)

<table>
<thead>
<tr>
<th>Formulation (%)</th>
<th>Pre extrusion (M_W (\times 10^6))</th>
<th>Post extrusion (M_W (\times 10^6))</th>
<th>% change</th>
<th>Drive current (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPM PEO 1M PEO 100K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A 20 70 10</td>
<td>1.050(\pm)0.028</td>
<td>0.958(\pm)0.024</td>
<td>-8.8</td>
<td>2.9–3.2</td>
</tr>
<tr>
<td>B 20 60 20</td>
<td>0.912(\pm)0.023</td>
<td>0.849(\pm)0.025</td>
<td>-6.9</td>
<td>2.8–3.2</td>
</tr>
<tr>
<td>C 20 40 40</td>
<td>1.135(\pm)0.016</td>
<td>1.084(\pm)0.018</td>
<td>-4.5</td>
<td>2.4–2.6</td>
</tr>
</tbody>
</table>

Unprocessed \(M_W\): PEO (1M) \(M_W=1.188\(\pm\)0.024.

Zone temperatures: 70°C, 85°C, 100°C, 105°C.
Screw speed: 20 rpm.
extrusion process resulted in polymer chains with a weight average near 100,000. Thus, the additional PEO 100K formed during processing was shown to plasticize the parent polymer. This observation was confirmed by a reduction in drive amperage.

The in vitro release properties of formulations A, B and C are presented in Fig. 6. The release rate of CPM from the extruded tablets was not significantly influenced by the presence of PEO 100K. Although PEO 100K hydrates more rapidly and has a lower viscosity than PEO 1M, the rate of CPM diffusion through the swollen gel layer did not change substantially.

CPM was found to be stable under the extrusion conditions studied. There was no change in HPLC retention time for the extruded samples and the drug was completely recovered in the dissolution media.

3.4. Influence of antioxidants

The thermal oxidation of PEO in the solid state has been characterized as an autocatalytic free radical process [15]. Antioxidants are often used to hinder oxidation reactions by scavenging free radicals. Antioxidants that have been used in pharmaceutical preparations include Vitamin E and its derivatives, Vitamin C (ascorbic acid) and butylated hydroxyanisole (BHA). Vitamin E TPGS is a water soluble derivative of natural Vitamin E. It is amphipathic and hydrophilic with surface active properties and has been used as an emulsifier, solubilizer and absorption enhancer. The influence of antioxidants on the hot-melt extrusion stability of PEO 1M matrix tablets containing CPM is presented in Table 2. The addition of 5% Vitamin E succinate, 1% Vitamin E and 30% Vitamin E TPGS successfully retarded molecular weight loss of PEO. The color of the extrudates was unchanged. These compounds have previously been found to suppress free radical production in photoirradiated pheomelanin [20]. In contrast, Vitamin C and BHA did not stabilize PEO.

Both Vitamin E succinate and Vitamin E TPGS decreased the torque during extrusion suggesting an improvement in polymer chain motion. The miscibility of Vitamin E Succinate and Vitamin E TPGS in PEO was studied by DSC (Fig. 3). The melting points of CPM, PEO 1M, Vitamin E TPGS and Vitamin E Succinate were found to be 135°C, 70°C, 38°C and 77°C, respectively. The melting point of Vitamin E TPGS can

![Fig. 6. Influence of low molecular weight PEO on CPM release from hot-melt extruded tablets using USP Method II at 37°C and 100 rpm in 900 ml purified water. Each point represents the mean ± standard deviation, n = 6. () 20% CPM, 80% PEO 1M, 0% PEO 100K, (○) 20% CPM, 70% PEO 1M, 10% PEO 100K, (□) 20% CPM, 60% PEO 1M, 20% PEO 100K, (>) 20% CPM, 40% PEO 1M, 40% PEO 100K.](image)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Post extrusion $M_W$ ($\times 10^6$)</th>
<th>% change</th>
<th>Drive current (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antioxidant</td>
<td>0.836±0.008</td>
<td>-11.3</td>
<td>3.0–3.4</td>
</tr>
<tr>
<td>0.5% Vitamin E succinate</td>
<td>0.828±0.005</td>
<td>-12.1</td>
<td>3.0–3.3</td>
</tr>
<tr>
<td>1.0% Vitamin E succinate</td>
<td>0.867±0.014</td>
<td>-8.0</td>
<td>2.8–3.4</td>
</tr>
<tr>
<td>5.0% Vitamin E succinate</td>
<td>0.917±0.019</td>
<td>-2.7</td>
<td>2.7–3.1</td>
</tr>
<tr>
<td>1.0% Vitamin E acetate</td>
<td>0.828±0.012</td>
<td>-12.1</td>
<td>4.3–4.9</td>
</tr>
<tr>
<td>5.0% Vitamin E acetate</td>
<td>0.826±0.039</td>
<td>-12.3</td>
<td>6.5–7.0</td>
</tr>
<tr>
<td>1.0% Vitamin E</td>
<td>0.916±0.027</td>
<td>-2.8</td>
<td>3.7–4.1</td>
</tr>
<tr>
<td>15.0% Vitamin E TPGS</td>
<td>0.843±0.025</td>
<td>-10.5</td>
<td>2.7–3.4</td>
</tr>
<tr>
<td>30.0% Vitamin E TPGS</td>
<td>0.907±0.026</td>
<td>-3.7</td>
<td>2.6–2.9</td>
</tr>
<tr>
<td>0.5% Ascorbic acid</td>
<td>0.730±0.102</td>
<td>-22.5</td>
<td>3.0–3.3</td>
</tr>
<tr>
<td>1.0% Ascorbic acid</td>
<td>0.626±0.076</td>
<td>-33.5</td>
<td>4.5–5.0</td>
</tr>
<tr>
<td>0.5% BHA</td>
<td>0.864±0.013</td>
<td>-8.3</td>
<td>3.4–3.7</td>
</tr>
<tr>
<td>1.0% BHA</td>
<td>0.874±0.009</td>
<td>-7.2</td>
<td>3.7–4.3</td>
</tr>
</tbody>
</table>

Unextruded PEO $M_W$ 0.942±0.021.
Zone temperatures: 70°C, 85°C, 100°C, 105°C.
Screw speed: 20 rpm.
be observed in the thermograms of the physical mixtures. Thermograms of the extrudates containing Vitamin E succinate, 15% Vitamin E TPGS and 30% Vitamin E TPGS demonstrate a decrease in the melting point of PEO of approximately 9°C, 9°C and 10°C, respectively. Thermal transitions corresponding to the melting points of Vitamin E succinate and Vitamin E TPGS were not observed in the extrudates. These results demonstrate that both Vitamin E succinate and Vitamin E TPGS were miscible with PEO in the melt and when incorporated into the PEO crystals, the Vitamin E derivatives did not recrystallize after the extrudate cooled.

Both butylated hydroxyanisole and Vitamin E acetate were ineffective in stabilizing the molecular weight of PEO during extrusion. The torque during extrusion was significantly increased. It was anticipated that the oily nature of Vitamin E acetate would function as a thermal lubricant during the extrusion process. In general, suitable solvents for polymers will chemically and physically resemble the structural repeat units of the polymer. If this situation exists, the adhesive forces between the solvent and polymer are similar to the cohesive forces between solvent molecules or between polymer molecules. An exchange of a solvent molecule by a polymer structural unit occurs with little change in the adhesive and cohesive forces. In the case of poor or unsuitable solvents, the cohesive forces between polymer molecules are more favorable. If this situation exists, the polymer chain reduces its hydrodynamic radius.

Other researchers have reported that the acetate anion caused PEO to salt out of aqueous solution [21]. The results of our study suggested that the residual acetate anions in Vitamin E acetate reduced the polymer radius in the molten state, increasing chain entanglements and consequently, the load required to move the polymer through the extruder.

The appearance of extrudates containing ascorbic acid changed from white to brown within 2 h. After extrusion, the molecular weight of PEO was considerably reduced and the polydispersity increased. McGary reported that strong acids reduced the solution viscosity of PEO [16]. Solutions of unprocessed PEO and ascorbic acid were prepared to examine whether the reduction in PEO molecular weight was the result of the extrusion process or a solution phenomenon (Table 3). The results from the solution study demonstrate that small quantities of ascorbic acid significantly reduced PEO molecular weight by an acid catalyzed chain scission reaction. However, it is also possible that the PEO degradation in solution with ascorbic acid is also accelerated by conditions during GPC analysis. It has been reported that ascorbic acid solutions undergo oxidation in the presence of air and are catalyzed by heat and traces of copper and iron [22].

<table>
<thead>
<tr>
<th>Formulation % (w/w)</th>
<th>$M_w$ ($\times 10^6$)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEO</td>
<td>Ascorbic acid</td>
<td></td>
</tr>
<tr>
<td>100.0</td>
<td>0</td>
<td>1.241 ± 0.008</td>
</tr>
<tr>
<td>99.9</td>
<td>0.10</td>
<td>1.119 ± 0.016</td>
</tr>
<tr>
<td>99.5</td>
<td>0.50</td>
<td>0.921 ± 0.038</td>
</tr>
<tr>
<td>99.0</td>
<td>1.00</td>
<td>0.788 ± 0.030</td>
</tr>
<tr>
<td>98.0</td>
<td>2.00</td>
<td>0.587 ± 0.019</td>
</tr>
</tbody>
</table>

Table 3 Influence of ascorbic acid on the solution stability of PEO 1M as measured by gel permeation chromatography (samples stored at 25°C for 12 h, ± SD, n = 3)

Fig. 7. Influence of antioxidants on the release of CPM from tablets using USP Method II at 37°C and 100 rpm in 900 ml purified water. Each point represents the mean ± standard deviation, n = 6. (◇) 20% CPM, 80% PEO 1M, direct compression, (○) 20% CPM, 50% PEO 1M, 30% Vitamin E TPGS Extrudate, (□) 20% CPM, 75% PEO 1M, 5% Vitamin E Succinate Extrudate, (△) 20% CPM, 80% PEO 1M Extrudate, (X) 20% CPM, 79% PEO 1M, 1% Vitamin E Extrudate.

The influence of the antioxidants on the release of CPM from extruded tablets and tablets prepared by direct compression is displayed in Fig. 7. All extruded formulations displayed comparable release rates. The release of CPM from tablets prepared by direct compression was more rapid than those prepared by hot-melt extrusion due to the increase in porosity and a decrease in tortuosity in the tablet compact. The formulation containing 30% Vitamin E TPGS released CPM more rapidly than the other formulations. Vitamin E TPGS is amphiphilic and can influence the release rate of CPM in two ways. Although the waxy, hydrophobic portion of the molecule can hinder the penetration of water into the tablet core, the hydrophilic portion of the molecule can reduce the gel strength of the PEO matrix and increase erosion during dissolution.
In this case, the latter is the dominant factor. The formulation containing 1% Vitamin E released CPM more slowly than all other formulations. The hydrophobic nature of Vitamin E delayed the penetration of water into the PEO matrix, resulting in a slower rate of gel hydration and formation.

4. Conclusions

The results of this study demonstrated that the thermal stability of PEO was dependent on both the storage temperature and the molecular weight of the polymer. Storage of the polymer above its melting point significantly increased its degradation. Polymer degradation when stored below its melting point is due to oxygen permeation in the amorphous region of the polymer.

PEO matrix tablets prepared by hot-melt extrusion were sensitive to both process temperature and screw speed. The mechanism of polymer degradation during extrusion is both thermal and mechanical. At very high screw speeds, degradation is due to melt fracture. The amperage consumed by the extruder motor drive can be used as an indicator of polymer stability.

The addition of PEO 100K improved processing of PEO 1M and did not significantly influence the rate of CPM release from matrix tablets. Vitamin E, Vitamin E succinate and Vitamin E TPGS were found to be suitable stabilizers for PEO during processing. Vitamin E succinate and Vitamin E TPGS were dispersed at the molecular level in hot-melt extruded tablets. Ascorbic acid was shown to degrade the polymer in solution. Drug release rates from hot-melt extruded tablets stabilized with antioxidants were dependent on the hydrophilic nature of the antioxidant.

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