Chemical Stabilization of a Δ9-Tetrahydrocannabinol Prodrug in Polymeric Matrix Systems Produced by a Hot-melt Method: Role of Microenvironment pH

Submitted: March 15, 2006; Accepted: May 21, 2006; Published: September 1, 2006

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ABSTRACT

This research was conducted in order to fabricate stable polyethylene oxide (PEO)-based transmucosal systems of a Δ^9-tetrahydrocannabinol (THC) prodrug, a hemisuccinate ester, using a hot-melt method. Since Δ^9-tetrahydrocannabinol-hemisuccinate (THC-HS) was heat labile, a series of processing aids were evaluated in order to facilitate hot-melt production at lower temperatures, thereby reducing THC-HS degradation. The stability of THC-HS was influenced both by the processing conditions such as heating time and temperature, and the postprocessing storage conditions. The type of formulation additive also affected the extent of degradation. In the presence of polyethylene glycol (PEG)-400, the percentage of relative degradation of THC-HS to THC was 13.5% and 49.4% at 80°C and 120°C, respectively. In contrast, incorporation of vitamin E succinate (VES) reduced processing degradation to 2.1% and 9.2%, respectively, under the same conditions. Severe degradation of THC-HS was observed during storage, even under freezing conditions (−18°C). A VES-Noveon AA-1 combination was observed to best stabilize the prodrug systems both during processing and postprocessing. Stabilization of THC-HS was achieved in these polyethylene oxide matrices at 4°C, with almost 90% of theoretical drug remaining for up to 8 months. Investigation of the pH effect revealed that the pH of the microenvironment in these polymeric systems could be modulated to significantly improve the stability of THC-HS, degradation being the least in a relatively acidic medium.

KEYWORDS: chemical degradation, hot-melt, pH microenvironment, plasticizers, polyethylene oxide, polymer, prodrug, Δ9-tetrahydrocannabinol-hemisuccinate.

INTRODUCTION

Δ^9-Tetrahydrocannabinol-hemisuccinate (THC-HS) is a prodrug form of Δ^9-tetrahydrocannabinol (THC). It is a light-yellow, viscous liquid that is sticky at room temperature and hardens upon refrigeration, suggesting that the glass transition temperature is below 25°C, thereby necessitating its storage under freezing conditions for stability purposes.[1] THC-HS (Figure 1) has a molecular weight of 414.53 and log P of 3.33 (Moriguchi's method), is sparingly soluble in water, and mostly acidic with a pK_a of 4.25 (ACD/Labs, Toronto, Ontario, Canada).

The parent compound, THC, is the major active cannabinoid, present in *Cannabis sativa*, exhibiting therapeutic potential in the treatment of nausea and vomiting during cancer chemotherapy, in appetite stimulation, cachexia associated with AIDS, glaucoma, analgesia, and other indications.[2] Although THC has demonstrated effectiveness in several medicinal applications, its efficacy via oral delivery is limited. It has been reported that the bioavailability of THC from the oral soft gelatin capsule formulation is low and inconsistent.[3,4] This phenomenon is mainly because of slow and erratic absorption (low solubility and/or permeability) and significant first-pass metabolism of the drug. Reliable, elevated plasma drug levels can be achieved by inhalation/smoking or IV delivery of THC[5]; however, these methods are not desirable.

Altering the characteristics of a compound by changing the molecular structure can improve the bioavailability and open new perspectives toward its therapeutic application. Thus, various cannabinoids with nonpsychotropic activity were synthesized, such as dexanabinol and its derivatives (including prodrugs) with increased solubility in water.[6] To overcome the pharmacokinetic limitations associated with THC, ElSohly et al[7,8] explored the utility of various ester prodrugs in suppository formulations as alternatives for effecting the systemic delivery of THC. Studies using the hemisuccinate ester (THC-HS) in a lipophilic base in dogs exhibited ~64% bioavailability. The authors reported that THC itself was not absorbed from the suppositories. Other esters were also studied, but the bioavailability was much lower than that of the hemisuccinate. Perlin et al[9] also examined the absorption of THC from different suppository formulations, in an effort to search for a better bioavailable formulation, and concluded that the compound would not be absorbed from either lipophilic or hydrophilic bases. Administration of THC-HS via suppositories, thus, resulted in higher, more consistent bioavailability and sustained plasma levels of THC. The advantages of this route of

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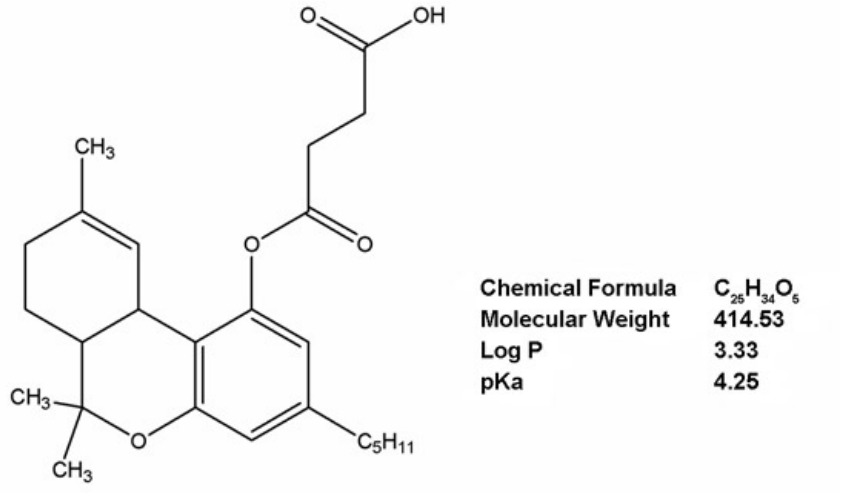

Figure 1. Structure of THC-HS.

administration seem clear, but it was thought unlikely to be popular in the United States, where suppository formulations have never been widely accepted.

Currently, there are only 3 references in the scientific literature[7,8,10] on THC-HS that are focused on studying the bioavailability of the drug in different suppository bases. Another study[11] investigated the kinetics of hydrolysis of N-methyl glucamine salt of Δ^8-tetrahydrocannabinol hemisuccinate in semi-aqueous solvents. A patent by ElSohly[12] describes the invention for formulating stable suppository systems for THC-HS. However, formulation and stability studies of the hemisuccinate ester prodrug of THC in any other dosage form have not been reported. Accordingly, this study was conducted in order to prepare stable polymeric films of the hemisuccinate ester for eventual use in buccal, sublingual, or other alternative routes.

Hot-melt processing has been demonstrated to be a viable technique for the preparation of drug-containing polymeric films.[13-15] In the present study, THC-HS was incorporated in the hot-melt fabricated polyethylene oxide (PEO) films intended for delivery through the buccal mucosa of the mouth. Because of the unique benefits offered by this route of drug delivery, development of a stable dosage form containing the hemisuccinate ester for buccal delivery is of significant importance as an alternative approach to rectal administration. A flexible transmucosal matrix system based on the mucoadhesive polymers, which adheres to the buccal mucosa for a predetermined period of time, is an appropriate dosage form for drug delivery through this route. For hot-melt processes, polymers with low glass transition or melting temperatures are the most desirable, owing to drug stability concern with high processing temperatures. The rationale behind selecting PEO as the base polymer was, therefore, its relatively low melt temperature (62°C-67°C), which requires processing temperatures of at least 110°C to 120°C for drug incorporation (due to high polymer melt viscosity at lower temperatures). PEO is also a thermoplastic polymer, which means that its polymer melt can be molded by conventional thermoplastic processing techniques. Indeed, these properties of PEO have been successfully used for the hot-melt extrusion processes,[14,16] wherein PEO was found to be a stable and suitable polymeric carrier for the drug substances. Other widely used polymers such as hydroxypropyl cellulose (HPC), Eudragits, and polyvinyl pyrrolidone (PVP) were also considered, but because of their higher melt temperatures they were not suitable for the hot-melt incorporation of the drug. For example, HPC softens at ~100°C to 110°C (processing temperatures above 140°C are required), while the tested Eudragits and PVP either did not soften or melt until 200°C under the processing conditions or were difficult to handle upon cooling. Based on these observations, PEO was selected as a viable polymer for fabrication into patches embedded with the drug.

The objective of this study was to fabricate stable polymeric dosage forms of THC-HS, using a hot-melt method. The research was focused toward stabilization of the prodrug in polymeric matrix systems for future applications in transmucosal delivery. Since the processing method used heat, stability of the ester both during processing and post-processing in the presence of various excipients/plasticizers was investigated. Studies were also conducted to elucidate the mechanism for the changes in the stability of the THC-HS observed, an understanding of which can be instrumental in the successful development of stable dosage forms containing THC-HS or other similar prodrug systems.

Materials and Methods

Materials

The following chemicals were used as obtained: Miglyol 812, 829, and 840 (Sasol Germany GmbH, Werk Witten, Germany); Capmul PG-8, PG-12, and MCM, and Captex

200 and 355 (Abitec Corp, Janesville, WI); Labrasol and Labrafil (Gattefosse, St Priest, France); triethanolamine (Fisher, Fairlawn, NJ); PEG-400, glyceryl monostearate, isopropyl myristate (IPM), diethyl phthalate, ethyl oleate, VES, almond oil, castor oil, light mineral oil, petrolatum, and butylhydroxy toluene (Spectrum Chemical Inc, New Brunswick, NJ); Tween 80 (Uniqema, Wilmington, DE); PEO-N10 (Sigma Aldrich, St Louis, MO); polycarbophil (Noveon AA-1, Noveon Inc, Cleveland, OH). High-performance liquid chromatography (HPLC)-grade water was freshly prepared in the laboratory (by Nanopure system, Barnstead, Dubuque, IA). HPLC-grade acetonitrile, methanol, and tetrahydrofuran were obtained from Fisher Scientific, Fair Lawn, NJ, and glacial acetic acid from J. T. Baker, Phillipsburg, NJ. THC-HS (in isooctane) and THC (in absolute ethanol) were provided by the ElSohly Laboratories Inc, Oxford, MS.

Methods

Preparation of Polymeric Matrices

A hot-melt cast molding method was used to fabricate powdered formulations into polymeric matrices incorporated with the drug.[17] The method involved heating the polymer with a processing aid or plasticizer until a molten mass was obtained. This melt was then homogenized with all other ingredients except the drug for ~15 minutes (step 1). The drug (in isooctane) was added to the molten mixture with constant mechanical stirring (step 2, during which the isooctane evaporated), followed by cooling under room conditions. For patch preparation using the above-stated hot-melt method, polymer:processing aid:drug ratio was 76:20:4. PEO-N10 grade (molecular weight [MW] 100 000) was the polymer used for all of the studies, unless stated otherwise.

Screening of Processing Aids/Plasticizers

PEO-N10 melts at ~62°C to 67°C; however, the nature of the polymer at 80°C to 120°C (high polymer melt viscosity) necessitates the use of a processing aid in order to produce a uniform mixture of the drug with the melt. For this purpose, various additives were tested to evaluate miscibility with PEO using a hot-melt method at 120°C (8:2 wt/wt polymer: additive ratio). The selection criterion was based on the miscibility of PEO with the additive during processing, which could be assessed by the ease in mixing of the molten mixture, and formation of a film with sufficient flexibility for handling purposes. Twenty-two potential additives including esters, oils, and surfactants were tested during this screening procedure. These were selected based on previous knowledge and literature data. Esters are known to decrease the melting point of polymers[15]; while the inclusion of oils or triglycerides (in suppositories) reduced the degradation of THC-HS.[12]

Differential Scanning Calorimetry

To assess the miscibility of the selected processing agents with PEO, ~5 mg of 8:2 wt/wt polymer:additive mixtures were weighed and sealed in aluminum pans, and then scanned using PerkinElmer Pyris-1 differential scanning calorimetry (DSC) instrument (PerkinElmer, Wellesley, MA). The samples were initially subjected to a heat-cool cycle to remove the thermal history of the samples (by heating to 100°C and holding for 10 minutes followed by cooling). A second heat cycle was initiated, wherein the samples were heated from 25°C to 200°C. The melting peak of PEO during the second heating cycle was determined to assess its miscibility with the additives. Nitrogen was used as a purge gas, at the flow rate of 20 mL/min, while the temperature ramp speed was 10°C/min for all of the studies.

Stability Studies

Effect of Processing Temperatures and Processing Aids on THC-HS Stability

THC-HS was incorporated into PEO matrix systems using the described hot-melt method. Two temperatures, 80°C and 120°C, were used to examine the effect of processing temperatures on the stability of THC-HS, and its extent of degradation during matrix fabrication. Three different heating times at step 2 (8, 12, or 15 minutes) were also employed to assess the influence of heating duration on prodrug degradation. Various processing aids were added to aid in the melting of the PEO and mixing of the overall melt. The fabricated matrices, upon cooling, were analyzed via HPLC to determine the extent of degradation of the hemisuccinate ester during processing.

Effect of Storage Temperatures and Processing Aids on THC-HS Stability

The THC-HS-containing PEO polymeric systems were stored at 4 different temperatures (−18°C, 4°C, 25°C, and 40°C) to investigate the effect of storage temperature on THC-HS stability. The film systems were analyzed at different time intervals to determine the amount of THC-HS and THC present, using a validated HPLC method. The stability of THC-HS in PEO-additive cast melts was compared with that in an additive-free PEO matrix. The results of THC-HS stability are expressed as a percentage of THC-HS degraded to THC at various time intervals. The amount of cannabinol (CBN), oxidative degradant of THC, formed in the patches was also included in the calculations.

Uniformity of Prodrug Degradation in the Polymer Matrix

A PEO polymeric system, incorporated with THC-HS, was prepared at 120°C using PEG-400 as the additive. Random

sites of the film were analyzed with HPLC for the amount of THC-HS and THC present, in order to determine if THC-HS distribution and its degradation to THC was homogeneous throughout the films.

Chromatographic Analysis

A weighed portion of the polymeric matrix containing THC-HS was dissolved in a known volume of tetrahydrofuran by sonicating for 10 to 20 minutes, depending on the formulation. The resulting solution was filtered, transferred into vials, and 20 μL was injected into the HPLC column for drug analysis.

A Waters HPLC-UV system (Waters Corp, Milford, MA) and a Luna 5μ C-18 (2), 150 × 4.60 mm column (Phenomenex, Torrance, CA), were used at a detection wavelength of 228 nm. The mobile phase consisted of 52% methanol, 30% acetonitrile, and 18% water with 0.75 mL acetic acid added per 1000 mL solvent. The flow was maintained at 1.8 mL/min, with THC-HS, THC, and CBN eluting within 15 minutes. This reversed-phase HPLC method was applicable for the analysis of THC-HS in the presence of its degradation products.[1] A calibration curve was constructed for THC-HS, THC, and CBN using a series of standard solutions of known concentrations, and the area under the peak was employed to determine the concentration of these in the sample solutions.

Moisture Sorption

In order to study the moisture uptake, the fabricated PEO matrices were stored in a 75% relative humidity (RH) chamber at 40°C. Saturated salt solution in contact with an excess of NaCl was used to achieve the desired humidity level in sealed humidity chambers. The experimental RH of the chamber was 79%. As a control, a portion of the patches was stored at 40°C and 0% RH. All of the patches were analyzed for chemical stability and moisture content using HPLC and thermogravimetric analysis (TGA), respectively, after 15 days of storage.

Perkin-Elmer Pyris-1 TGA was used to determine the moisture content of the samples. The samples were heated from 30°C to 90°C at a heating rate of 40°C/min and held at 90°C for 20 to 30 minutes until no more weight loss (<0.1%/h) was observed. All TGA runs were performed in an open pan with purge and protective nitrogen gas flow at 40 mL/min.

Apparent pH of the Polymeric Patch Formulations

Approximately 0.5 g of the patch was caused to swell and dissolve to form a gel by sonicating it with 0.5 mL of nanopure water (pH 6.6 ± 0.05) for 30 minutes. The pH was recorded by immersing the electrode into the gel matrix and allowing it to equilibrate for 1 minute.

Data Analysis

Statistical analysis was performed using Microsoft Excel. A *t* test was used to analyze the results, and a statistically significant difference was considered when $P < .05$.

Results and Discussion

To investigate the compatibility between PEO and THC-HS, drug-polymer matrices were prepared at 120°C and stored at 4 predetermined temperatures. Figure 2 illustrates the drug degradation in the presence of PEO, as analyzed at different temperatures and time points. It was found that 8.4% of the prodrug degraded during the process of incorporation using the hot-melt method. This may indicate drug instability or chemical interaction between THC-HS and PEO at the temperatures used for the hot-melt processing or both. Degradation of the ester drug also occurred at all of the storage temperatures. Owing to relatively high viscosity of the polymer melt at the temperature used during processing, more stirring time was required to disperse the drug throughout the matrix, thereby exposing the drug to a high temperature for an extended time. The addition of a plasticizer or processing aid could lower the melt viscosity, processing temperature, and time, thus potentially improving the stability of the ester prodrug.

Screening of Processing Agents

The addition of plasticizers or processing aids decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer

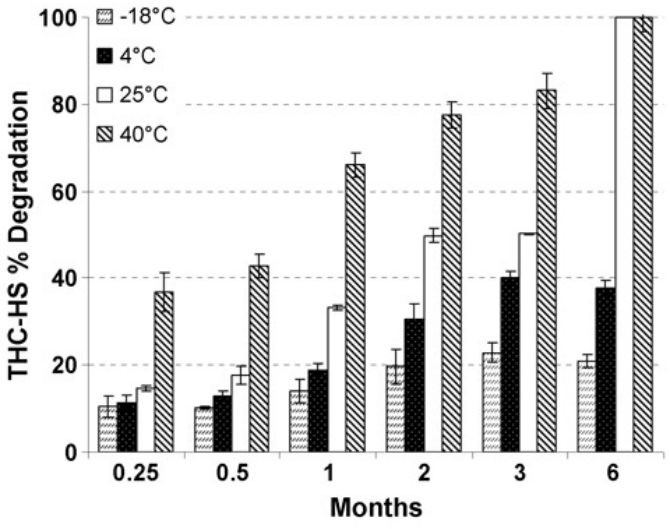

Figure 2. Stability of THC-HS in the presence of PEO at 4 different temperatures: −18°C, 4°C, 25°C, and 40°C. The matrices were prepared by heating the drug with PEO at 120°C, (n = 3).

chains.[15,18,19] The use of these agents during film fabrication lowers the processing temperatures considerably, thereby improving the processing stability of both the polymer and the drug.[20]

In order to lower the polymer melt viscosity, processing temperatures and hence drug degradation, various potential plasticizers/additives were screened to evaluate their miscibility with PEO using a hot-melt temperature of 120°C. The results of the miscibility tests with PEO are shown in Table 1. The selection criterion was based on the miscibility of PEO with the additive during processing, which could be visually assessed by the ease in mixing of the molten mixture and the formation of a film with sufficient flexibility for handling purposes. Twenty-two potential additives were tested during this screening procedure, of which 4 were selected to aid the incorporation of THC-HS in the polymeric matrices. These included VES, PEG-400, IPM, and Capmul PG-12 (CPG).

Miscibility of the selected processing agents with PEO was further evaluated using DSC analysis. Peak for the pure PEO melt transition occurred at ~63.7°C, during the second heat cycle. Upon blending with PEG, CPG, and VES, the melting point of PEO decreased to 55.9°C, 60.2°C, and 60.0°C, respectively. Decrease in the melting point of PEO indicates the miscibility of the polymer, with these excipients in the melt,[21] which could be of pharmaceutical importance in the processing of heat-labile drugs. Although, DSC scans of the PEO-IPM blends depicted no change in the melting point of PEO (64.3°C), IPM was selected as a potential processing aid based on the fact that it could lower the polymer melt viscosity during film fabrication. When using these selected additives, it was found that the processing temperatures of PEO for film fabrication could be lowered to 80°C.

Effect of Processing Conditions on THC-HS Stability

Since the film fabrication method involved heat, it was necessary to investigate the effect of heating time and temperature to which the drug was exposed. In the method used, PEO and the processing aid were initially heated at the desired temperature for ~20 minutes (step 1) before adding the drug, which was further heated for a specified duration (step 2).

To determine the effect of heating duration, the formulation PEO-PEG-(THC-HS) was heated at 120°C, and the time of heat application at step 2 was varied from 8 minutes to 15 minutes. The results indicated that the ester drug was highly unstable to heat in the formulation used. As expected, increase in the heating duration increased the degradation of THC-HS considerably (41.5% ± 4.4%, 45.1% ± 1.4%, and 56.3% ± 3.1% degradation using 8-, 12-, and 15-minute heating time, respectively). It was also observed that the stability of the ester under the hot-melt conditions was poor.

Table 1. Screening of Potential Processing Aids or Plasticizers for Polyethylene Oxide*

Group/Type	Additive	Miscibility With PEO†
Fatty acid esters	Miglyol 812, 829, 840	Immiscible
	Capmul PG-12	Miscible; waxy film
	Capmul PG-8, MCM	Miscible; brittle film
	Captex 200	Miscible; brittle film
	Captex 355	Immiscible
	Glyceryl Monostearate	Immiscible
	Isopropyl myristate	Miscible; waxy film
	Ethyl oleate	Miscible; difficult handling
Ester	Vitamin E Succinate	Miscible; good film
Phthalate ester	Diethyl phthalate	Miscible; difficult handling
Glycol derivative	PEG-400	Miscible; good film
Glycerides/Lipoidic vehicle	Labrasol	Miscible; difficult handling
Glycerides/oil	Labrafil	Immiscible
Alkanolamines/surfactant	Triethanolamine	Immiscible
Tween/surfactant	Polysorbate 80	Miscible; difficult handling
Oils	Almond oil	Immiscible
	Castor oil	Miscible; difficult handling
	Light mineral oil	Immiscible
Hydrocarbon	Petrolatum	Immiscible

*PEO indicates polyethylene oxide. Selection of the additives was based on the ease in mixing of the melt (by heating the additive with PEO at 120°C) and formation of a flexible film.

†The terminology "good film/waxy film/brittle film" is representative of the handling characteristics of the polymeric matrices and is not indicative of the physico-chemical characterization. This terminology is presently used only for the selection of processing aids for PEO and hydroxypropyl cellulose.

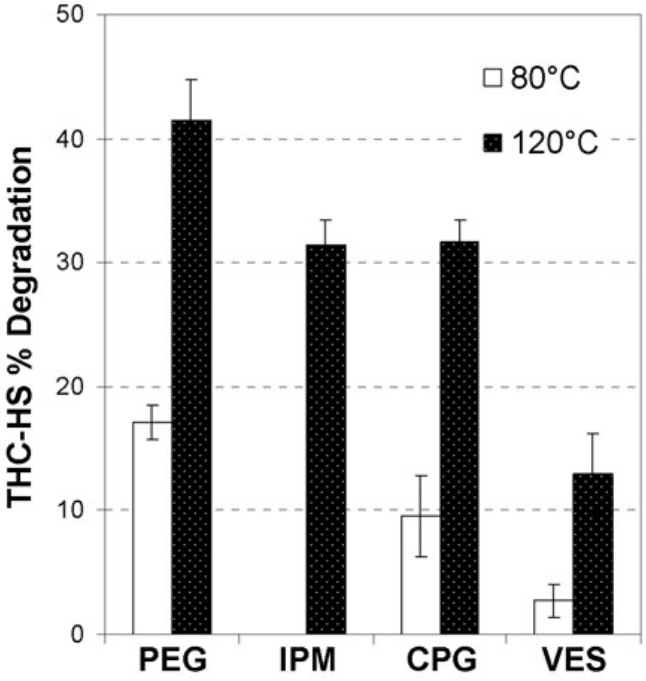

Figure 3. Effect of hot-melt processing temperature on THC-HS degradation in the presence of various processing aids. The heating time at step 2 of the hot-melt process was maintained at 8 minutes, (n = 3).

The effect of processing temperature (80°C and 120°C) on the stability of THC-HS is illustrated in Figure 3. The heating time at step 2 was maintained at 8 minutes. The extent of degradation of the ester during processing was assessed in the presence of selected processing aids (PEG, IPM, CPG, and VES). The results indicate that the fabrication temperature also influenced the degradation of the hemisuccinate ester. Degradation was considerably higher at 120°C, as compared with 80°C, in presence of all of the selected additives. PEO matrix fabrication was not possible in presence of IPM at 80°C; therefore no data were obtained for this processing temperature. Incorporation of THC-HS in the matrices in the presence of PEG was deleterious for the drug. Degradation was lower when IPM or CPG were used as processing aids and was significantly less with VES.

Increasing the heating time and/or temperature facilitated the stirring of the molten mass during the fabrication process, which was also accompanied by a considerable increase in drug degradation. Thus, film formation was easier at 120°C owing to a decrease in the melt viscosity and ease in mechanical stirring, but degradation was higher than that at 80°C in all of the cases. It was also noticed during matrix formation that at least 8 minutes of heating was needed at step 2 at either of the 2 temperatures to mix the drug and form an acceptable film with uniform drug distribution. Without the use of a processing aid, the PEO-drug mixture had to be heated for a longer duration to obtain a film with adequate drug distribution uniformity. As discussed previously, longer heating durations resulted in higher degradation of the hemisuccinate ester. Therefore, addition of the processing agents during the polymer matrix fabrication was necessary to successfully obtain a THC-HS-incorporated film using the optimum heating duration and temperature. These findings demonstrate that the stability of the ester drug can be modulated by process parameters and formulation additives and that high throughput can be achieved.

Uniformity of Prodrug Degradation in the Polymer Matrix

Each fabricated polymeric patch was divided into sections and stored at different temperatures for chemical stability analysis. To ensure that the THC-HS content (and degradation) was uniform throughout the patch, a PEO polymeric matrix was fabricated using PEG-400 as the processing aid at 120°C. Analysis of random sites of the film suggested that the conversion of the prodrug to the parent was uniform throughout the matrix system. The percentage degradation of THC-HS averaged 45.1% ± 1.4% varying from 42.9% to 46.8% in different sites of the patch (absolute deviation varied from −2.2% to 1.7%).

Effect of Processing Aids and Storage Temperatures on THC-HS Stability

Based on the preliminary data obtained above, PEO matrices were fabricated with the drug at 80°C and 8 minutes of heating time at step 2 to evaluate the effects of the selected processing aids on the stability of THC-HS in the matrices during storage. Figure 4 depicts the stability of the prodrug in the presence of PEG, suggesting extensive degradation. The graph included only 2 storage conditions, namely, refrigerating (4°C) and freezing −18°C) conditions, as complete degradation was observed in the polymeric systems stored at the other temperatures within 2 weeks (70.2% and 80.5% degradation at 25°C and 40°C, respectively, after 1 week). The system was so unstable that even at −18°C THC-HS degradation continued. Owing to such high chemical instability of the drug in PEO matrices at low temperatures, the formulation goal of the present research was to stabilize the drug at 4°C, in addition to elucidating the mechanism of its degradation. These results are in accordance with those of the previous studies, wherein THC-HS was unstable in hydrophilic suppository bases both during preparation and storage at temperatures as low as 4°C.[12]

Figure 4 also illustrates the stability of THC-HS in the polymeric matrix using CPG as the processing aid. The ester was relatively stable when compared with the PEG systems; however, degradation still occurred at 4°C. Under freezing conditions, although degradation was insignificant,

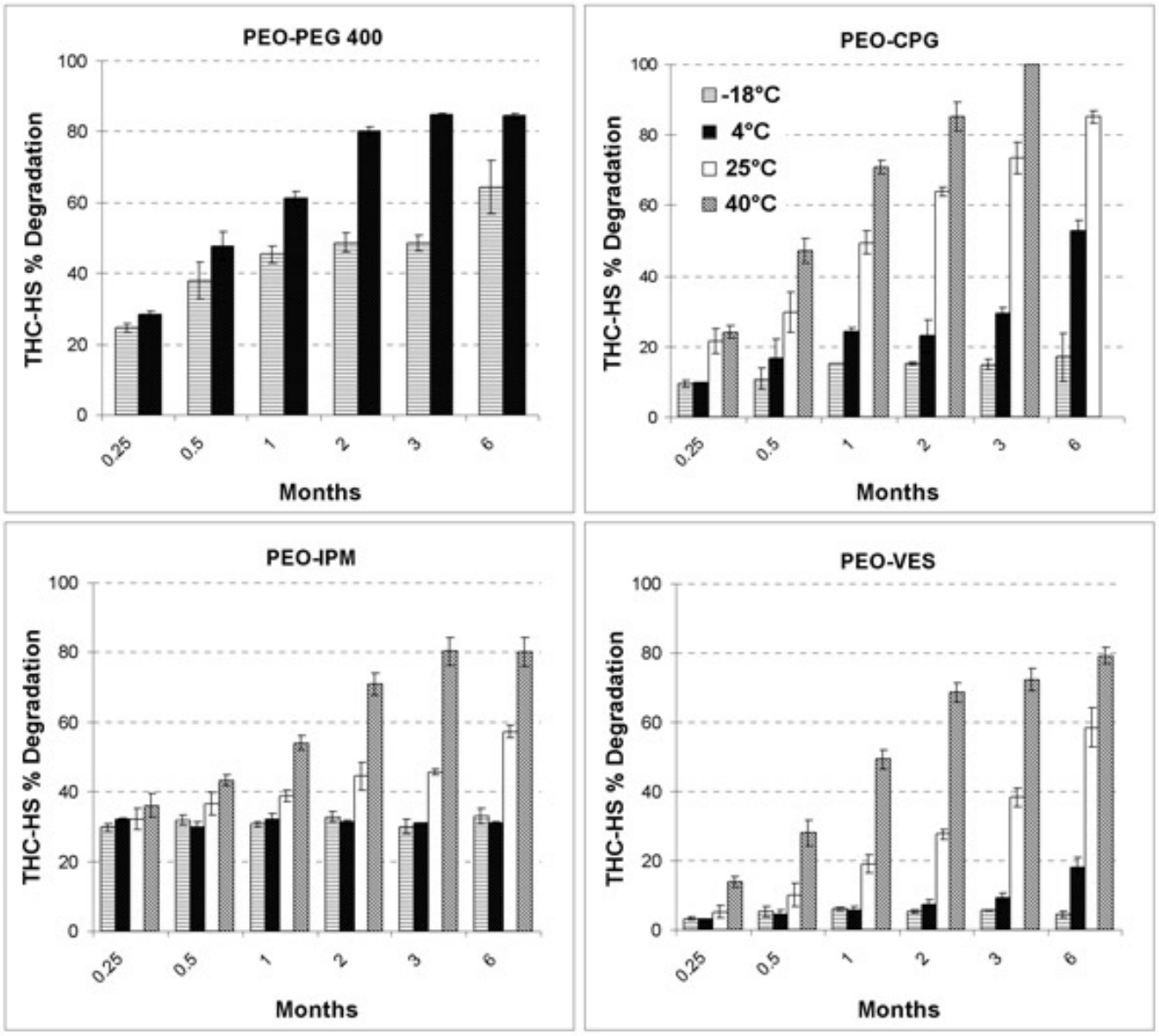

Figure 4. Stability of THC-HS in PEO-PEG-400, PEO-CPG, PEO-IPM, and PEO-VES patches stored at 4 different temperatures: −18°C, 4°C, 25°C, and 40°C. The patches were prepared by heating the formulations for 8 minutes at 80°C at step 2 of the hot-melt process (except PEO-IPM patches, which were prepared at 120°C), (n = 3).

considerable loss of drug had already occurred during processing (9.6%). Missing bar in the figure indicate near 100% degradation of the ester. Stability of THC-HS in the IPM processed patch at 120°C is also depicted in Figure 4. Film fabrication with IPM was not possible at 80°C, and processing at higher temperature produced a considerable loss of drug (31.4%) during processing itself. Storage of the film at −18°C and 4°C produced no further degradation of the drug for up to 6 months. In contrast, degradation continued at 25°C and 40°C. THC-HS was relatively stable in the VES-containing formula, as summarized in Figure 4. Drug degradation during processing was also the least (2.7%) in the presence of VES as a processing aid. No significant degradation occurred at the storage temperature of −18°C. Less than 10% of the drug was observed to be degraded at 4°C for up to 3 months.

Based on the results obtained, subsequent fabrication of THC-HS in PEO polymeric matrices was performed using VES as the processing aid, and an attempt was made to further stabilize the drug in the dosage form prior to in vivo studies. A flexible transmucosal matrix system, based on the mucoadhesive polymers that adhere to the buccal mucosa for a predetermined period of time, is an appropriate dosage form for drug delivery through the buccal mucosa. Mucoadhesives impart bioadhesivity to the buccal delivery systems to withstand salivary and musculatory activity. In the present study, Noveon AA-1 was selected as the mucoadhesive

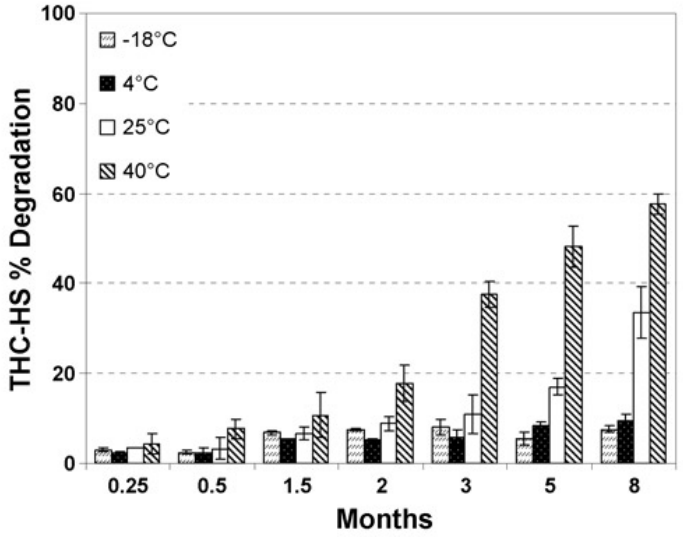

Figure 5. Stability of THC-HS in PEO-VES-Noveon patches stored at 4 different temperatures: −18°C, 4°C, 25°C, and 40°C. The patches were prepared by heating the formulations for 8 minutes at 80°C at step 2 of the hot-melt process, (n = 3).

polymer for incorporation into the polymeric matrices. Noveon is a high MW polymer of acrylic acid, cross-linked with divinyl glycol, and has been successfully incorporated in bioadhesive drug delivery systems.

In view of the high instability of THC-HS in the polymeric systems, it was pertinent to study the chemical behavior of the drug in the environment containing Noveon. To investigate this, the drug was dispersed in the molten mass formulated with PEO-VES-Noveon at 80°C. The results depicted in Figure 5 interestingly indicate further stabilization of the ester, both during processing and postprocessing. The amount of THC-HS remaining after processing was more than 98.5%, which was higher than what was achieved with VES alone. At least 90% of the drug remained in the patch after 8 months of storage at 4°C, and for 3 months at 25°C. In summary, earlier studies in PEO-PEG formulations exhibited 80% degradation at 4°C within 2 months. With a combination of PEO with VES and Noveon, degradation of THC-HS was thus significantly reduced and a sufficiently stable polymeric dosage form was produced.

The rate of degradation can vary dramatically from days to months depending on the nature of the drug products, dosage forms, processing conditions, and handling and storage conditions. Although considerable chemical degradation of the drug occurred while processing with PEG, CPG, and IPM, it was relevant to conduct stability studies at different storage temperatures and time intervals in order to gain an insight into the rate and mechanism of degradation of THC-HS in these polymeric systems. Degradation of the ester drug in PEO-only matrices occurred at all of the storage temperatures but was relatively slower than in the presence of PEO-PEG and PEO-CPG combinations. This result may indicate that these additives may be synergistically increasing the degradation of THC-HS, both during processing and postprocessing.

The plot of the percentage drug degradation versus time yielded a linear relationship corresponding to a pseudo first-order degradation mechanism of THC-HS in the polymeric systems ($r^2 \approx 1$). The degradation rates of THC-HS, calculated from the slopes of the linear fits, are listed in Table 2. The degradation rate constants of THC-HS in the polymeric films increased upon addition of PEG and CPG at 40°C (as compared with PEO alone), indicating synergistic degradation effects. Rate constants were the lowest for PEO-VES-Noveon systems. The Arrhenius plots of the ester degradation in various tested formulations are depicted in Figure 6. The polymeric systems exhibited linear fit ($r^2 > 0.95$) over the experimental temperature range, except for the PEO-VES-Noveon system. The apparent Arrhenius plot parameters (A and E_a) for the ester hydrolysis, obtained from fitting the linear regions of the data in Figure 6, are summarized in Table 3. Activation energy was the highest for the PEO-VES system, which correlates well with the stabilization effect in this particular formulation, as opposed to the other processing aid-containing systems. The most stable system, PEO-VES-Noveon, however, exhibited a low activation energy contrary to its maximum

Table 2. Pseudo First-order Degradation Rate Constants of THC-HS in the Polymeric Films, as a Function of Temperature*

Pseudo First-Order Degradation Rate Constants, wk^{-1}				
	Storage Temperature			
Polymeric Film With THC-HS	−18°C	4°C	25°C	40°C
PEO	0.0147	0.0363	0.0783	0.1223
PEO-PEG	0.0271	0.1394	1.0232	1.4467
PEO-CPG	0.003	0.0256	0.0711	0.227
PEO-IPM	0.0013	0.0027	0.0185	0.1077
PEO-VES	0.0001	0.007	0.0353	0.1054
PEO-VES-Noveon	0.0018	0.0033	0.0082	0.0341

*THC-HS indicates Δ^9-tetrahydrocannabinol-hemisuccinate; PEO, polyethylene oxide; PEG, polyethylene glycol; CPG, Capmul PG-12; IPM, isopropyl myristate; VES, vitamin E succinate; and Noveon, polycarbophil.

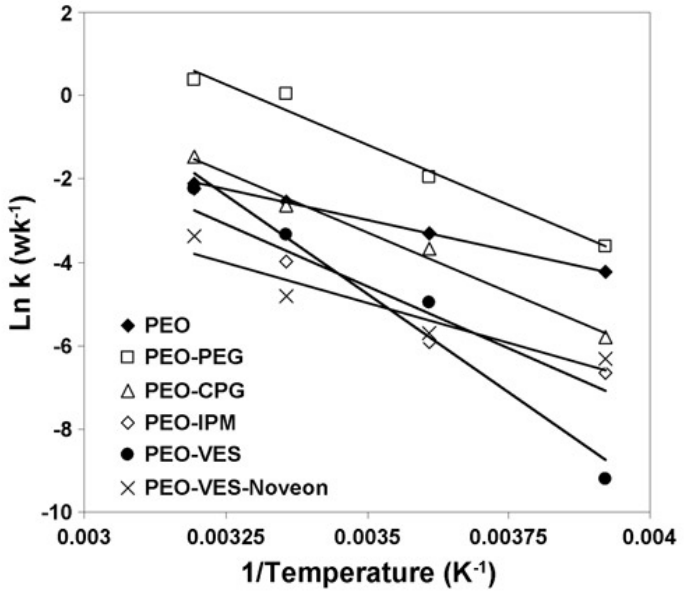

Figure 6. Arrhenius plots of the degradation of THC-HS in the polymeric films.

stabilization role. The fact that the frequency factor was low (less chemical interaction) and that this is a multicomponent system might be the possible reasons for the low rate of drug degradation and deviation from linearity.

A review and comparison of the hydrophilic and lipophilic properties of the processing aids indicate that CPG, IPM, VES, and Noveon are relatively lipophilic in nature. Consequently, the stability data suggested that THC-HS may be more prone to degradation in the presence of hydrophilic excipients such as PEG and PEO, suggesting the possibility of chemical interaction between the prodrug and various excipients. This observation was also made by ElSohly[12] who reported extensive degradation of THC-HS in hydrophilic suppository bases, such as Witepsol, with little degradation in hydrophobic bases, such as paraffin.

In addition, examination of the HPLC chromatograms obtained in the present study depicted only one pronounced degradation peak—that of parent THC—indicating that instability of THC-HS in PEO matrices during processing and storage is most likely the result of hydrolysis of the ester bond. This hydrolytic reaction may be owing to the presence of moisture in the matrices or possible interaction of the ether and hydroxyl groups of PEO (and/or other additives) with the drug molecules via hydrogen bonds, thereby causing hydrolysis of the ester. Stabilization of THC-HS in the polymeric systems was thus aimed at preventing the substantial hydrolysis of the THC prodrug ester derivative to THC in the formulated dosage form.

Hydrolytic reactions in the solid state are believed to occur only in the adsorbed moisture layer.[22] The available water controls the rate of the reaction as the drug is always saturated in this layer.[23] The moisture content and chemical stability of the patches stored at 0% and 75% RH are depicted in Figure 7, which indicated that adsorption of small amounts of moisture (at 75%) resulted in a significant increase in drug degradation. PEO-PEG patches exhibited a similar extent of drug degradation, although the moisture content of the systems stored at 75% RH was significantly higher than that of the control (suggesting that the role of chemical interaction cannot be disregarded). The total moisture in the PEO sample before processing was ~0.5%, which remained unchanged in the processed PEO-only films (not shown). Still degradation of THC-HS was considerable in the presence of PEO, again indicating the role of chemical interaction. In addition, considerable degradation of the control samples, together with the fact that the samples for stability studies (at 4 temperatures) were stored below 20% RH, suggested that moisture may not be the primary or only factor affecting the instability of THC-HS. Chemical interaction between the formulation components and the drug could also be contributing to the instability of the prodrug during and after processing. Chemical interaction can occur at the points of contact between the drug and excipient particles as has been suggested in other studies.[24,25] ElSohly suggested that the possible hygroscopic nature of the suppository bases was not the source of drug instability.[12] The inclusion of materials that prevent water adsorption from the air (which can hydrolyze the ester) did not enhance the stability of the ester.

Effect of Microenvironment pH

A factor that could have a major effect on the solid-state stability and chemical interaction of drugs such as THC-HS is the microenviromental pH, to which the drug is exposed in a solid dosage form. Microenvironmental pH can significantly affect the performance of a formulation by altering key properties such as solid-state stability (chemical and/or physical), dissolution, and release profiles.[26] Buffering is commonly used in such solid formulations based on the

Table 3. Summary of the Kinetic Parameters From Arrhenius Plots for the Degradation of THC-HS in the Polymeric Matrices*

Polymeric Film With THC-HS	Frequency Factor, ln A, wk^{-1}	Activation Energy, E_a, kcal/mol
PEO	2.14	5.82
PEO-PEG	13.95	11.49
PEO-CPG	11.74	11.44
PEO-IPM	11.29	11.91
PEO-VES	23.19	18.77
PEO-VES-Noveon	3.27	7.59

*THC-HS indicates Δ^9-tetrahydrocannabinol-hemisuccinate; PEO, polyethylene oxide; PEG, polyethylene glycol; CPG, Capmul PG-12; IPM, isopropyl myristate; VES, vitamin E succinate; and Noveon, polycarbophil.

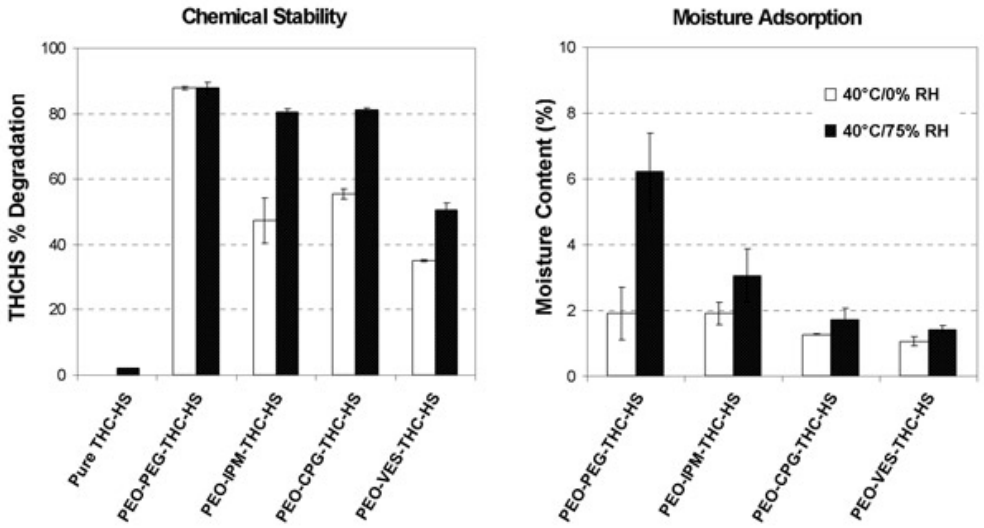

Figure 7. Chemical stability and moisture adsorption of the PEO matrices prepared at 80°C and stored for 15 days at 40°C/75% RH and 40°C/0% RH, (n = 2).

system characterization in the solution. Studies on the use of pH modifiers to decrease the degradation rate of an ester prodrug, by adjusting the microenvironmental pH to ~4.0, in the solid-state has been previously reported.[26,27] The ester prodrugs of a synthetic cannabinoid, dexanabinol, hydrolyzed rapidly at basic pH (9.0), while stability increased considerably at an acidic pH (1.2).[6] The base-catalyzed hydrolysis was much faster than that of the acid-catalyzed reaction.

To observe the pH effect on the stability of the THC ester, the pH of the polymeric systems were determined for any significant pH differences. The pH of the patches without the drug is reported in Table 4, which indicates that the most stable patch formulation (PEO-VES-Noveon) corresponded to the most acidic microenvironment. This finding suggests a role of pH on the ester stability and chemical interaction (ester hydrolysis). Thus, a possible approach that could be employed for the stabilization of THC-HS in polymeric films is through the adjustment of the microenvironmental pH to an appropriate acidic range. To test this hypothesis, control of the microenvironmental pH was attained by adding an acidic component, namely, citric acid monohydrate (CAM), to the PEO-CPG systems (which displayed intermediate instability relative to others) at 80°C and subsequently adding THC-HS. This patch was stored at 40°C and analyzed at different time intervals for drug degradation. Addition of the acidifying agent to the patch formulation not only decreased the drug hydrolysis during hot-melt processing but also considerably improved the stability of THC-HS at the elevated storage temperature.

Table 4. Apparent pH Values of the Polymer Patch Formulations (without THC-HS)*

Polymer Patch Formulation	Observed pH
Water	6.4
PEO	7.3
PEO-PEG	7.6
PEO-CPG	7.5
PEO-IPM	7.5
PEO-VES	5.6
PEO-VES-Noveon	4.6

*THC-HS indicates Δ^9-tetrahydrocannabinol-hemisuccinate; PEO, polyethylene oxide; PEG, polyethylene glycol; CPG, Capmul PG-12; IPM, isopropyl myristate; VES, vitamin E succinate; and Noveon, polycarbophil. The patch was caused to swell and form a gel by sonicating in presence of water. The pH values of the gel were recorded.

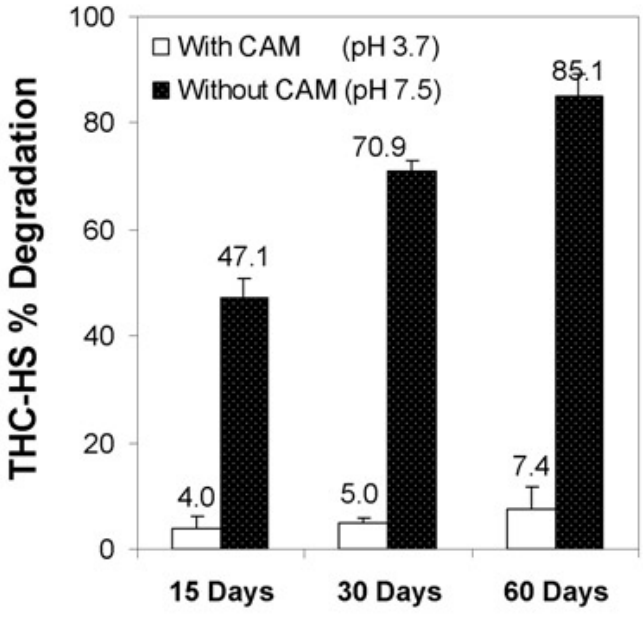

Figure 8. Stability of THC-HS in pH-adjusted PEO-CPG patches stored at 40°C. (CAM is the acid constituent citric acid monohydrate). The patches were prepared by heating the formulations at 80°C, (n = 3).

Drug degradation during fabrication was determined to be only 0.2% with CAM, while it was as high as 9.6% without the use of the acidifying agent.

The effect of pH is clearly evident in Figure 8, which displays the percentage THC-HS degradation in the patches with and without CAM at 40°C. Only 7.4% of the ester drug degraded in the pH-adjusted patch as compared with 85.1% in the control patch after 60 days of storage at the temperature that was previously shown to be highly unfavorable to THC-HS stability. The degradation rate constant of the ester in the pH-adjusted patch (at 40°C) was determined to be 0.0105 wk^{-1}, which is 21-fold less than that in the control patch (0.227 wk^{-1}). It seems that hydrolysis of the ester bond was influenced by deprotonation of the carboxyl group at pHs higher than the acid dissociation constant (pK_a = 4.25).[28] Adjustment of the microenvironment pH below the pK_a of the drug decreased ionization (and solubility) and significantly reduced the chemical interaction (between the drug and water or hydroxyl-containing excipients) that generally led to hydrolysis of the hemisuccinate ester bond. Thus, controlling the pH of a selectively stable formulation could considerably enhance the stability of the ester in the polymeric films at 25°C. Furthermore, the stability of THC-HS may be optimized in these types of formulations by determining a pH-stability profile for the drug and adjusting the microenvironmental pH of the formulated product to balance stability and future patient acceptability needs.

CONCLUSIONS

The heating time and temperature, and the type of processing aid or plasticizer included in the formulation played an important role in the hot-melt processing of the PEO dosage forms and in regulating the drug degradation. Among the additives studied, VES-Noveon AA-1 combination was observed to best stabilize the prodrug systems both during processing and postprocessing. The microenvironment pH of the polymeric systems could be modulated to considerably improve the stability of THC-HS, degradation being the lowest in an acidic environment. Stability of the ester prodrug could therefore be optimized in the solid-state by altering the formulation ingredients and by the use of an appropriate agent that adjusts the microenvironmental pH of the product close to the pH of maximum stability.

ACKNOWLEDGMENTS

The authors would like to thank ElSohly Laboratories Inc and the National Center for Natural Products Research for supplying THC-HS and THC for this study. This work was partially supported by the following grants from the National Institutes of Health, Bethesda, MD: 1R41 GM067304-01 and P20RR17701.

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