Published in final edited form as:

J Pharm Sci. 2006 November ; 95(11): 2473–2485. doi:10.1002/jps.20711.

Polymeric Systems for Amorphous Δ^9 -Tetrahydrocannabinol Produced by a Hot-Melt Method. Part II: Effect of Oxidation Mechanisms and Chemical Interactions on Stability

MANISH MUNJAL¹, MAHMOUD A. ELSOHLY^{1,2}, and MICHAEL A. REPKA^{1,2}

¹Department of Pharmaceutics, School of Pharmacy, The University of Mississippi, University, Mississippi 38677-1848

²Research Institute of Pharmaceutical Sciences, The University of Mississippi, University, Mississippi 38677-1848

Abstract

The objectives of the present research investigations were to (i) elucidate the mechanism for the oxidative degradation of Δ^9 -tetrahydrocannabinol (THC) in polymer matrix systems prepared by a hot-melt fabrication procedure, and (ii) study the potential for controlling these mechanisms to reduce the degradation of THC in solid dosage formulations. Various factors considered and applied included drug-excipient compatibility, use of antioxidants, cross-linking in polymeric matrices, microenvironment pH, and moisture effect. Instability of THC in polyethylene oxide (PEO)-vitamin E succinate (VES) patches was determined to be due to chemical interaction between the drug and the vitamin as well as with the atmospheric oxygen. Of the different classes and mechanisms of antioxidants studied, quenching of oxygen by reducing agents, namely, ascorbic acid was the most effective in stabilizing THC in PEO-VES matrices. Only 5.8% of the drug degraded in the ascorbic acid-containing patch as compared to the control (31.6%) after 2 months of storage at 40°C. This coupled with the cross-linking extent and adjustment of the pH microenvironment, which seemed to have an impact on the THC degradation, might be effectively utilized towards stabilization of the drug in these polymeric matrices and other pharmaceutical dosage forms. These studies are relevant to the development of a stable transmucosal matrix system for the therapeutic delivery of amorphous THC.

Keywords

Δ^9 -tetrahydrocannabinol; drug-excipient compatibility; polymeric matrices; hot-melt processing; amorphous; vitamin E succinate; oxidation; stability; formulation pH; cross-linking; anti-oxidants; ascorbic acid

INTRODUCTION

It is well established that Δ^9 -tetrahydrocannabinol (THC) is a highly unstable drug. A previous communication discussed the preliminary results on the investigation of various processing and post-processing factors influencing the stability of THC in polymeric matrices, prepared using hot-melt method.¹ The extent of degradation was influenced by several factors such as the type of additive used, film-forming condition and film storage temperature. An attempt was made in the study to modulate the processing conditions to

improve the drug throughput. While it was found through the thermal investigations that THC weight reduction occurred in a linear fashion, when held at 160 or 200°C, blending with polyethylene oxide (PEO) controlled the weight loss. Based on this data and the melt temperature of PEO, processing temperature of 120°C was determined to be favorable for all the formulation components. THC was particularly unstable in the vitamin E succinate (VES) processed matrices. It would be important both from the scientific and pharmaceutical perspective to understand the mechanism of THC degradation in this particular polymer matrix, which would be helpful in stabilizing the drug in these and other dosage forms.

Stability of THC has been a subject of several investigations; however, extensive research has not been conducted to understand the mechanism of degradation in solid dosage formulations. Indeed, one of the most important aspects for the formulation of THC dosage forms is to overcome the stability problem. Presence of cannabinol (CBN), the thermo-oxidative degradation product of THC, in the material is indicative of drug degradation by oxidation. Chemical structures of THC and CBN are depicted in Figure 1. A drug can undergo oxidative degradation by a number of mechanisms. The oxidizing species may be inadvertently introduced in to the drug product through excipients or under various storage conditions. Peroxides may be present in the polymers when used as initiators and cross-linking agents during manufacturing.² Polymeric excipients containing polyether linkages can easily undergo free radical autoxidation generating hydroperoxides, which can further produce oxidizing hydroxyl and peroxy radicals, usually with the aid of certain metallic ions.^{3,4} For example, polyethylene glycols, polyoxyethylene nonionic surfactants (Tween-80), PEOs and polyvinylpyrrolidone can rapidly autoxidize during storage and handling at room temperature, and can be potential sources of oxidizing species in solid formulations when used as plasticizers, surfactants or permeability enhancers.⁵⁻⁷ Hartauer et al.⁸ demonstrated the oxidation of raloxifene HCl in the tablet formulation by the presence of hydroperoxide in povidone and croscopovidone.

If specific oxidants are known to promote drug degradation in a pharmaceutical formulation, strategies may be employed to scavenge or eliminate these particular oxidizing species. Free radical initiation and autoxidation can be slowed down by minimizing exposure to light or heat, or with appropriate packaging or storage conditions (such as under nitrogen).⁷ These approaches, however, may not be practical for the pharmaceutical products.

There are a variety of antioxidants, which are capable of opposing or preventing the breakdown of active ingredients by the process of oxidation, and can be incorporated into the formulations that contain oxidation-prone actives. The use of anti-oxidants, in pharmaceutical dosage forms for the protection of drugs against the loss of therapeutic effectiveness by oxidation, began as early as 1940s.⁹ Antioxidants have the ability to inhibit or slow chain reaction oxidative process at relatively low concentrations. This property of the antioxidant substances is of considerable importance to the pharmaceutical formulator because of the large number of chemically diverse medicinal agents known to undergo oxidative decomposition.⁹ Antioxidants are most effective in stabilizing oxygen-sensitive drug formulations when they are oxidized instead of the drug, and yet not oxidized so rapidly that they are quickly consumed. Commonly used antioxidants include phenols (butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and propyl gallate), thiols, ascorbic acid and ascorbyl palmitate. Metal chelators, such as ethylenediaminetetraacetic acid (EDTA), citric acid, malic acid, and fumaric acid, function by forming complexes with transition metal ions such as Cu^{2+} and Fe^{3+} that catalyze oxidation. These antioxidants and metal chelators can be incorporated in the solid dosage formulations using common formulation techniques.

Although solid-state autoxidation plays an important role in drug decomposition, it has not been studied adequately. Plenty of information on oxidative mechanisms and reactions in liquid pharmaceutical formulations (due to the presence of excipient impurities) can be found in the chemical literature. However, only few detailed studies have been performed on the reactions occurring with specific drugs in solid formulations.¹⁰ This lack of pharmaceutically relevant data leads to poor predictive capabilities of drug oxidation and largely empirical utilization of antioxidants in formulations.¹⁰ Thus, only through experimentation (such as by accelerated stability testing) can the effectiveness of an antioxidant, to stabilize a formulation, be determined.

This research discusses in detail the methods utilized to formulate and stabilize THC in a polymeric solid dosage formulation, prepared by a novel hot-melt fabrication method. Studies were designed to understand and elucidate the role of various mechanisms in influencing the drug stability in different polymeric systems, which were evaluated in the earlier research communication. These experiments would also be functional in identifying the source and mechanism of oxidation, so that a strategy could be developed to inhibit or reduce oxidation of THC in the polymeric formulations. Several approaches were followed to inhibit the oxidation reaction and stabilize the drug and formulation, namely compatibility studies, microenvironmental pH, cross-linking, and the use of anti-oxidants in the polymeric dosage forms. An understanding of the role of these factors in THC degradation may be applied for the successful development of stable dosage forms containing the active cannabinoid.

EXPERIMENTAL

Materials

The following chemicals were used as obtained: Capmul PG-12 (Abitec Corp., Janesville, WI); polyethylene glycol-400, VES, BHT, BHA, propyl gallate, EDTA, ascorbic acid, sodium citrate dihydrate (Spectrum Chemical Inc., New Brunswick, NJ); PEO—N10, ferrous sulfate heptahydrate (Sigma Aldrich Inc., St. Louis, MO); Noveon AA-1 (Noveon Inc., Cleveland, OH).

HPLC-grade water was freshly prepared in the laboratory (by Nanopure systems, Barnstead, Dubuque, IA). HPLC-grade acetonitrile and methanol and were obtained from Fisher Scientific, Fair Lawn, NJ; glacial acetic acid was obtained from J. T. Baker, Phillipsburg, NJ. ElSohly Laboratories, Inc., Oxford, MS provided the THC (in absolute ethanol) and CBN samples.

METHODS

Preparation of Polymeric Matrices

A hot-melt casting method used to fabricate polymeric matrices incorporated with the drug is described in detail in the earlier paper. In brief, the polymer was heated together with a processing aid or plasticizer until a molten mass was formed. This melt was homogenized with other ingredients except the drug for approximately 15 min (Step I). The drug (in absolute ethanol) was added in the resultant molten mixture with constant mechanical stirring (Step II, during which the ethanol evaporated), followed by cooling under room conditions. The final product, obtained upon cooling, was a flexible polymeric patch with an evenly distributed drug. Due to the highly viscous nature of the polymer melt, various additives were selected for the formation of a film with sufficient flexibility. These included VES, Capmul PG-12 (CPG) and polyethylene glycol-400 (PEG). PEO-N10 (MW 100,000) was the polymer used for all the studies, unless stated otherwise.

Studies for Identification of Source of THC Oxidation in Polymeric Matrices

To identify the source and mechanism of THC degradation (oxidation) in polymeric systems, various approaches were employed as depicted in Figure 2. These included (i) compatibility studies of THC with various excipients in binary mixtures, (ii) stability of THC in the presence of increasing proportions of PEO, (iii) stability of THC in the presence of increasing proportions of VES, (iv) stability of THC in PEO-VES patches, wherein PEO and VES were heated for a longer duration of time at Step I, and (v) incorporation of different classes of antioxidants in PEO-drug patches. Studies (ii) and (iii) were conducted to investigate for the presence of any oxidizing impurities in these excipients, as PEO was the base polymer used and VES inclusion enhanced THC degradation. If oxidation is related to the highly reactive impurities present in the excipients, then drug instability usually shows itself in the form of greater decomposition rates for more dilute drug mixtures.¹¹ To investigate the possibility of oxidizing species being generated upon heating the polymers, and influencing the stability of THC, study (iv) was conducted. Inclusion of different classes of antioxidants in the matrices (Study v) could elucidate the oxidation mechanism affecting the active's stability, in these systems. All of the samples prepared for the aforementioned stability studies were stored at 40°C, and analyzed for up to 2 months.

Incorporation of Antioxidants

Different classes of antioxidants were incorporated in the PEO matrices, along with the drug to investigate the role of various oxidation mechanisms on THC degradation. For this purpose the PEO-VES-THC film fabrication was conducted at 120°C, and the processed matrices were placed at 40°C for the accelerated stability testing. Three classes of antioxidants were utilized: (i) free radical scavengers (BHT, BHA, and propyl gallate), (ii) metal scavengers (EDTA), and (iii) oxygen scavengers or reducing agents (ascorbic acid, ferrous sulfate). THC content in the matrices was analyzed after 1 and 2 months, utilizing the HPLC method.

Apparent pH of the Patch Formulations

Approximately 0.5 mg of the patch was allowed to swell and dissolve to form a gel by sonicating it in contact with 0.5 ml of nanopure water (pH 6.6 ± 0.05) for 30 min. The apparent pH was recorded by immersing the electrode into the gel matrix and allowing it to equilibrate for 1 min.

Sample Preparation for Analysis

A weighed portion of the polymeric drug-containing matrix was dissolved in a known volume of methanol by sonicating for 10–20 min, depending on the formulation. The resulting solution was filtered, transferred into vials and injected into the HPLC column.

HPLC Analysis

THC and CBN content in the samples were analyzed by HPLC (Waters) and by UV detection (Waters) at a wavelength of 228 nm. The stationary phase was a Luna 5 μ C-18 (2), $150 \times 4.60 \mu$ column. A mobile phase of methanol:acetonitrile:water (52:30:18) adjusted to pH 4.5 (by adding 0.75 ml acetic acid per 1000 ml) was used with the flow rate of 1.8 ml/min. The 20 μ l samples were injected for the analysis. This reversed phase HPLC method was applicable for the analysis of THC in the presence of its decomposition products.¹² A calibration curve was constructed for both 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 THC and CBN 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 $79 \pm 1.4\%$. As a control, patches were also stored at 40°C and 0% RH. All the formulations were analyzed for the chemical stability and moisture content using HPLC and thermogravimetric analysis, respectively, after 15 days of storage.

Thermogravimetric Analysis (TGA)

Moisture content of the samples was determined using a Perkin-Elmer Pyris-1 TGA instrument. Seven to eight milligrams samples were heated from 30 to 90°C at a heating rate of 40°C/min, and held at 90°C for 20–30 min until no more weight loss was observed, as depicted by the TGA curves. All TGA runs were performed in an open pan with purge and protective nitrogen gas flow at 40 ml/min.

RESULTS AND DISCUSSION

In the previous investigation, it was observed that THC degraded to a relatively higher extent in VES processed matrices. Elucidating the degradation mechanism of the active in this unstable system may bring forth strategies that could be employed for THC stabilization, not only in the polymer films used in this study, but also in other solid dosage forms. In the present research, we have utilized the PEO-VES system and studied the role of various factors on drug degradation. These included the drug-excipient compatibility, use of antioxidants, cross-linking in polymeric matrices, microenvironment pH, and moisture effect.

It is well known that mono- and polyetheric compounds, in particular polyoxyethylene oxides, easily undergo free radical autoxidation to form hydroperoxides which can be a source of drug degradation by oxidation in pharmaceutical formulations.^{7,13} Additionally, in the case of PEOs, a high-molecular weight material is prepared and then oxidatively degraded to give the desired molecular weight range.¹¹ This degradation generally leads to peroxides and other low-molecular weight species. Although, THC was quite stable in PEO-PEG and PEO-CPG systems, it was important to understand the mechanism behind its degradation in PEO-VES systems.

Drug-Excipient Compatibility

To assess the compatibility between THC and other formulation excipients, 80:20 excipient:drug mixtures were prepared (by heating at 120°C for 1 min) and stored at 40°C. The excipients included VES, CPG, PEG, and PEO. The results, depicted in Table 1, in general indicated a decrease in the THC degradation upon blending with any of the selected excipient, as compared to the pure drug. THC was relatively stable in the presence of PEO and PEG. This may be attributed to the encapsulation of the drug within these polymers, as was discussed previously in Part I of the investigation. The extent of degradation observed in the CPG mix may be due to lesser encapsulation and also heat and air instability of the drug. Since, THC was reasonably stable in PEO-CPG matrices upon storage, this system was not studied as profoundly as the VES-containing systems. Indeed, the drug was highly unstable in the VES mix (48.1% lost after 1 month of storage at 40°C), which could account for the high-degradation rate of THC in the PEO-VES matrices, observed in the previous communication. This particular mix also depicted an increase in the content of CBN which is known to be the major oxidative decomposition product of THC.

VES may not be able to encapsulate THC sufficiently, thereby exposing the drug to air oxidation. To further confirm this, VES:THC 80:20 mixtures were prepared by heating at 120°C for 1 min, and then stored in the presence of oxygen or nitrogen. Blends heated and stored in the oxygen atmosphere were labeled as THC-VES-O₂, while those in the nitrogen atmosphere were labeled as THC-VES-N₂. All the samples were stored at 25 and 40°C, and analyzed after 1 month for the extent of THC degradation. THC-VES-O₂ and THC-VES-N₂ samples at 25°C depicted 18.0±0.3% and 9.5±0.8% degradation, respectively, proving that THC oxidation could not be prevented by mixing with VES, or that VES did not encapsulate THC sufficiently. In contrast, PEO-THC-O₂ and PEO-THC-N₂ (80:20) mixtures prepared and stored under the same conditions depicted 2.3±0.3 and 2.1±0.5% degradation of the drug (at 25°C after 1 month), respectively, further strengthening the concept that VES may not be able to encapsulate THC. It was found that the storage temperature of 40°C caused equivalent drug degradation in the samples, and might be too high to examine for any significant differences between the samples. Inability of the VES to encapsulate the drug (leading to air oxidation) or chemical incompatibility between the two (due to impurities in VES) might be the possible reasons for the observed degradation of the drug, in the VES-THC blends.

Stability of THC in Increasing Proportions of PEO and VES

The results for studies (ii) and (iii) are demonstrated in Table 2. It is expected that an increase in the polymer content would cause increased degradation of the drug, if oxidation is due to the presence of oxidative impurities. PEO-THC binary mixtures were prepared by heating at 120°C (as this might induce oxidizing species) in different ratios and placed for stability testing. Similarly, different ratios of VES and THC in a binary mixture were prepared for the stability studies.

As depicted by the stability data, increase in PEO content did not increase the extent of degradation. In fact, more degradation was observed at lower polymer ratios. Thus, it was hypothesized that the presence of oxidizing impurities, if any, in PEO did not affect the THC decomposition. In contrast, analysis of the VES:THC mixtures demonstrated higher drug degradation with increased VES content. Analysis of CBN content revealed that its level in the binary mixtures also increased with the amount of VES. CBN formation in studies (i–iii) suggests that the oxidative instability of the drug in binary mixtures as well as in patches might be due to a chemical interaction/incompatibility between THC and VES (leading to oxidation of the active), air oxidation or the presence of an oxidizing impurity in VES.

Effect of Heating Duration at Step I on THC Stability

The oxidizing impurities in VES, if any, may be present or generated during the heating process of patch fabrication. Stress treatment such as excessive heating of the excipients might be useful in entailing these impurities as the source of oxidative instability. Subsequently, heating times of 15 and 45 min were employed for PEO-VES-THC patch fabrication at 120°C. These heating durations refer to the initial heating periods that only PEO and VES were subjected to (Step I of the hot-melt method). If any oxidizing species were generated during processing, this method would identify them, that is, the patch in which PEO-VES were heated for more time should depict higher instability of THC. No significant differences were observed in the THC stability after 2 months, in the patches prepared by employing different heating times. The extent of drug degradation in the patch, which was heated for 15 and 45 min, was 20.1 and 18.9%, respectively. This may suggest that the processing conditions did not induce the formation of oxidizing agents in VES. Based on these studies there are two possibilities by which THC may be experiencing oxidation. Firstly, the oxidizing species such as free radicals or metal ions might already be present in the VES and secondly, THC and VES might be undergoing chemical

incompatibility. Additionally, in the polymeric film formulations there is the probability of drug instability occurring due to air oxidation depending on the cross-linking extent and air diffusion. These factors, henceforth, were later studied and reported.

Effect of Antioxidants

Next to hydrolysis and solvolysis reactions, oxidation is the main cause for drug instability. There are a number of mechanisms by which a pharmaceutical active can undergo oxidation in a delivery system in the presence of various excipients. The drug may be oxidized by the reactive impurities present, or generated in these excipients, in addition to the reaction by free radicals in the presence of oxygen (autoxidation) or by electrophilic or nucleophilic oxygen addition.⁷ Oxidizing impurities may be sometimes added during polymer manufacturing or generated upon exposure of the excipient or formulation to light, heat, or transition metals. Trace metals, which are oxidized by a one-electron transfer process, are most active in catalyzing drug oxidation. Metals can also react directly with oxygen and with hydroperoxides to form free radicals which could initiate the chain reaction of autoxidation.⁹

To investigate the possibility of oxidation by oxidizing species in VES or atmospheric oxygen, various antioxidants were incorporated into the PEO-VES-THC patches (because the source of oxidation was VES) at 120°C and placed on accelerated stability study at 40°C. Understanding the mechanism of oxidation together with trial experimentation is also an effective means of selecting the appropriate antioxidant for formulating a stable drug product. Only a few studies have reported the specific use and levels of antioxidants required to prevent drug degradation in solid dosage formulations.⁷ The relative order of effectiveness of individual antioxidants can vary widely with the system, especially in complex formulations. pH, trace metals, peroxide content as well as the drug and excipients can influence the relative effectiveness. The amount of antioxidant needed is usually determined empirically.¹⁵

The antioxidants selected in the present study were the ones that inhibit oxidation by different mechanisms. Antioxidants that inhibit free radical initiation and propagation are the free radical scavengers (chain terminators or true antioxidants) and include BHT, BHA, tocopherols, etc. The inclusion of DL- α -tocopherol stabilized fenprostalene by preventing the oxidation of hydroperoxide intermediates formed during polyethylene glycol decomposition.¹⁶ Metal scavengers, such as EDTA, can be added to slow the formation of free radicals by complexing metals that catalyze free radical initiation. Oxygen scavenger class of antioxidants (e.g., ascorbic acid) that deplete oxygen in closed systems is also widely used in pharmaceutical systems. If the oxidizing impurities, that are already present in the excipient, do not have the potential to increase during processing or storage, then ferrous sulfate can be used to reduce and prevent further oxidation. The antioxidants utilized in this study to understand the mechanism of THC oxidation are listed in Figure 2.

The effectiveness of these antioxidants in controlling THC degradation is illustrated in Table 3, which lists the percent THC degraded in the patches after one and 2 months of storage at 40°C. Of the various classes of antioxidants investigated, only ascorbic acid decreased the oxidative degradation of THC in the polymeric matrices. All other patches exhibited the extent of instability similar to the patch without any antioxidant (control). Propyl gallate containing patch induced the highest decomposition of THC. Usually, the more antioxidant added, the more protection it offers, however, higher antioxidant concentrations of propyl gallate have been reported to accelerate oxidation.¹⁷ Since, phenolic antioxidants were not effective in inhibiting the oxidation, it may be assumed that the peroxy radicals were not significantly involved in the oxidation chain reaction.

Trace metals, as discussed earlier, can play a major role in initiating autoxidation reactions. A particularly effective strategy to slow autoxidation in such cases is to add a chelating agent to the formulation. The most effective chelator for use in pharmaceutical products is EDTA. Inefficacy of EDTA in retarding the THC degradation suggested that the autoxidation reaction by trace metals was not significant. The possibility of the presence (or role) of oxidizing impurities in VES may be further undermined based on the fact that ferrous sulfate failed to control THC oxidation. Therefore, chemical interaction wherein VES and/or oxygen (from the environment) extract electrons from THC molecules seems to be the main mechanism causing oxidation of the drug.

Only 5.8% of THC degraded in the ascorbic acid-containing patch as compared to the control (31.6%). Since, ascorbic acid is an oxygen scavenger type of antioxidant, there might be a possibility that VES films have higher permeability and allow greater air diffusion, or that VES has a lower oxidation potential than the drug. Presence of ascorbic acid might be interfering with the oxidation process by consuming the oxygen during processing and storage. These preventive types of antioxidants are sacrificial reductants or preferentially oxidized compounds which are oxidized more readily than the drug because of the higher standard oxidation potential. They effectively scavenge oxygen while being consumed themselves. This strategy can be especially effective in systems where the amount of oxygen present is limited (due to packaging).¹⁴ Antioxidants of this type can be effective without intimate contact with the drug since they lower the oxygen level in the environment.

Inhibition of drug autoxidation by addition of ascorbic acid can occur by several possible mechanisms. In the presence of trace metals, ascorbate monoanion reacts rapidly and consumes oxygen. This is usually considered the primary mechanism for this antioxidant, especially in closed systems.¹⁵ Ascorbic acid is also known to chelate metal ions at high concentrations, and act as a chain breaking antioxidant. Additionally, if there is a chemical interaction between THC and VES, ascorbic acid might be interfering with this process.

Synergism is known to improve the activity of antioxidants, so a combination of antioxidants with ascorbic acid, in a formulation of THC, would probably enhance the antioxygenic behavior of this antioxidant. Combination of ascorbic acid and a phenolic antioxidant (BHT, BHA) have shown synergism in some applications.¹⁸

Effect of Cross-Linking in Polymeric Matrices

Molecular oxygen from the atmosphere has been shown to react with organic crystals,¹⁹ the reactivity depending on the crystal form and morphology, which governs the permeability and solubility of oxygen in the matrix. THC is an amorphous drug which means it has greater mobility and lacks crystal-lattice stabilization energy, thereby, permitting higher oxygen solubility and permeability. This also facilitates electron transfer to oxygen, thereby, stimulating the oxidation reaction.¹¹ Processing environment (i.e., air or nitrogen) has been reported to affect the stability of THC over time. Several injection formulations of THC when sealed in glass ampoules under nitrogen atmosphere were more stable than those sealed under room air.²⁰ In the case of polymeric systems, the extent of cross-linking between the formulation components can affect the air diffusion and movement in the films.^{21–23} The ability of ascorbic acid (oxygen scavenger) in controlling the oxidative degradation of THC also suggests the possibility of higher air diffusion in PEO-VES systems that may further lead to higher oxidation of the drug.

PEO consists of ether and hydroxyl groups which are capable of interacting with the plasticizer and processing aid molecules *via* hydrogen bonds. The selected additives have different molecular structures and a number of functional groups for hydrogen bonding. They are expected to show different extents of interaction with PEO which can have an

important influence on oxygen permeation and mobility in the polymeric film. This factor is capable of influencing the degradation of THC in different polymer film formulations. This being the case, the degree of cross-linking in PEO-VES systems should be less than in other formulations. Lower cross-linking would allow relatively higher diffusion and permeability of oxygen into the matrix system, thereby causing more interaction between the oxygen and drug molecules, leading to oxidative decomposition during storage. In contrast, other patches that might have more cross-linking would not allow easy diffusion of air through it. Air may permeate into the matrix but to a lesser extent causing low level of degradation. Some air might even get trapped in the matrix system during fabrication procedure that may react with the drug during storage. Most laminating resins, gel coats and other polyester resins entrap air during processing and application. Entrapment of air in porous structure of the polymer films has been reported.²⁴

Although, at higher hot-melt temperatures it is expected that there would be less dissolved oxygen (air) in the melt, it is thought that air could get entrapped during cooling, leading to degradation over time. Thus, it would be of interest to examine what effect air or nitrogen processing could have on the stability of an oxidation-sensitive drug such as THC. Studies were conducted to investigate whether the presence of VES has any effect on air diffusion and/or entrapment. PEO-VES-THC patches were prepared and stored either in the presence of air or nitrogen as depicted schematically in Figure 3, and analyzed for up to 2 months for the THC amount degraded. For these oxidative degradation studies to be purposeful, appropriate controls were also prepared in order to get a better understanding of whether the degradation resulted from a thermal, free-radical, or non-free-radical process. Thus, pure THC was also placed under the same conditions, that is, at 40°C under nitrogen (THC-N₂) and air (THC-Air).

Patch I was exposed to air during processing and storage, while it was attempted to minimize air exposure of Patch IV throughout the study. Highest level of degradation is expected in Patch I and lowest in Patch IV. If air entrapment leads to oxidation during storage then similar extent of degradation should occur in Patches I and III. Alternately, if degradation in Patch III is same as in Patch IV, it would indicate no air entrapment. If decomposition in Patch II is same as in I, it would suggest permeation of the atmospheric gas, may it be air or nitrogen, and thus a low level of cross-linking. The results after 2 months of storage are illustrated in Figure 4, which depicts higher decomposition of pure THC in the presence of air than in the nitrogen environment. As already mentioned, THC stability is also influenced by heat (storage temperature of 40°C), as determined by the percent degradation in nitrogen atmosphere.

HPLC analysis of the patches immediately upon fabrication indicated similar extents of degradation, which was negligible at less than 0.2%. Thus, processing atmosphere did not affect the stability of THC during fabrication procedure. Stability data after 2 months depicted similar extent of degradation in Patches I and II, suggesting air diffusion in the polymeric systems. Degradation of THC in Patch IV (not exposed to air) was the least as expected. Significant differences in stability of THC in Patches I and III (and similar degradation in Patches III and IV), suggests no air entrapment during processing. The low extent of cross-linking in PEO-VES-THC matrices indicates higher air permeation in and out of the system. Previously it was established that VES failed to effectively encapsulate THC and reduce its air degradation/oxidation. Higher air permeation into the PEO-VES-THC matrices would allow more drug-oxygen interaction (since not all of THC is encapsulated), thereby resulting in a higher drug degradation. This study suggests that the extent of cross-linking in a polymer matrix could have a possible role in affecting the permeability of air through it, and, thus the stability of an oxidation-sensitive drug such as THC.

Effect of Microenvironment pH

Chemical interactions in the solid-state and, hence, stability of a pH-sensitive drug, in dosage forms, could be significantly affected by the microenvironment pH to which the drug is exposed. Modulation of the microenvironment pH was effective in controlling the degradation of one of the ester pro-drugs (hemisuccinate) of THC, in the polymeric matrices (unpublished results). Buffering is commonly used in such solid formulations based on the system characterization in the solution. Badawy et al.^{25,26} found that the stability of their compound in the solid-state could be improved by the use of appropriate acids (disodium citrate, citric acid, monobasic sodium phosphate etc.), that adjusts the microenvironmental pH to approximately 4. Drooge et al.²⁷ has also reported on the possible role of pH in the stabilization of THC in inulin glass dispersions. These authors found that THC remained unaffected in solid dispersions prepared from solutions of pH 6 or pH 9, but degraded substantially if prepared by freeze drying a solution at pH 3. In the present study, pH of the polymeric systems, without the drug, was examined (Table 4). Data indicated that the pH of the most unstable PEO-VES patch was in the acidic range, while those of the stable formulations was in the neutral range. It is worthwhile to mention that another formulation containing a bioadhesive Noveon™ AA-1 (PEO-VES-Noveon; pH 4.6) exhibited higher instability than PEO-VES formulations (pH 5.6).

Based on these observations, it was thought that the pH microenvironment in the polymeric patches could be a potential factor affecting the stability of THC. Thus, a possible approach that could be applied for the stabilization of THC in the polymeric films is through alteration of the microenvironmental pH and adjusting it in the basic or neutral range. To test this hypothesis, a polymeric formulation PEO-VES-THC containing a basic buffer, sodium citrate dehydrate (NCD), was fabricated into a patch and stored at 40°C to investigate whether the pH control could stabilize the drug. The pH of this patch was recorded to be 6.5.

The results of THC stability in pH-adjusted patch as compared with the control are illustrated in Figure 5. Adjusting the pH microenvironment exhibited a significant stabilization effect on THC degradation. pH-adjusted patches depicted $25.1 \pm 1.3\%$ THC loss after 2 months of storage at 40°C as compared to the control ($32.0 \pm 1.7\%$).

Effect of Moisture Adsorption by Polymeric Matrices

Moisture content of the PEO matrices (Fig. 6) stored at 75% RH and the controls (0%) suggested that VES patches adsorbed minimal moisture from the atmosphere but exhibited maximum instability, which was similar under both the conditions. Lower moisture adsorption, in addition, would also allow greater permeability of oxygen into the matrix, thus facilitating the solid–gas reaction between the drug and oxygen. This is because the presence of water on the surface of a solid usually retards oxidation by reducing the available surface area, if oxidation is only a solid–gas reaction.¹⁵ Indeed, it was found that the pure THC when stored at higher RH degraded to a lesser extent than when stored at lower RH (unpublished results). PEO-CPG systems did not adsorb moisture at any of the conditions either. PEO-PEG matrices exhibited more than 3.0% moisture uptake, but exhibited only marginal drug degradation. These studies suggested that moisture content did not play a significant role in THC degradation. Additionally, the solid-state instability of THC in VES-containing systems was therefore due to chemical incompatibility/interaction between the two, and also with the molecular oxygen from the atmosphere, for which ascorbic acid was determined to be the most effective anti-oxidant.

CONCLUSIONS

In summary, the findings in the present study demonstrated the complex nature of interactions involving the stability of THC in the polymeric systems. Since the final dosage form is a complex matrix of polymeric, organic and inorganic solids each with vastly different physicochemical properties, it is difficult to study the oxidation mechanisms in pharmaceutical dosage forms. The fact that (i) THC is amorphous in nature, and is prone to degradation by heat, air, and light, (ii) the polymeric systems allow diffusion of air through the intricate network of the cross-linked matrix, and (iii) one of the basic limitations of antioxidants is their inability to completely prevent the oxidative degradation of a drug, further complicated the investigations. Of the various classes of antioxidants utilized to study the mechanism of oxidation on THC decomposition in the polymeric patches, an oxygen scavenger type, ascorbic acid, proved to be effective in stabilizing the drug against oxidative degradation. Thus, oxygen diffusion into the polymeric films from the environment (which is dependant on the cross-linking) as well as chemical interaction between THC and VES were determined to be the major mechanisms behind the oxidative decomposition of the drug in PEO-VES systems. The efficacy of ascorbic acid coupled with the modulation of the microenvironment pH (which proved to have some effect on the stability) might unfold new strategies in improving the stability of THC in dosage forms. While the earlier communication was based on modulating the hot-melt processing conditions by studying the thermal and chemical stability of THC, this present research was an attempt to recognize the mechanism that has a major impact on the stability of this unique drug in polymeric matrices.

Acknowledgments

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

REFERENCES

1. Munjal M, Stodghill SP, ElSohly MA, Repka MA. Polymeric systems for amorphous Δ^9 -tetrahydrocannabinol produced by a hot-melt method. Part I: Chemical and thermal stability during processing. *J Pharm Sci.* 2006; 95:1841–1853. [PubMed: 16795020]
2. Mageli, OL.; Sheppard, CS. Organic peroxides and peroxy compounds-general description.. In: Swern, D., editor. *Organic peroxides.* 1st Edition. Wiley-Interscience; New York: 1970. p. 1-104.
3. McGary CW. Degradation of poly(ethylene oxide). *J Polym Sci.* 1960; 2:51–57.
4. Donbrow, M.; Schick, MJ. Stability of the polyoxyethylene chain. nonionic surfactants. 2nd Edition. Dekker, Inc.; New York: 1987. p. 1011-1072.
5. Hamburger R, Azaz E, Donbrow M. Autoxidation of polyethylene non-ionic surfactants and of polyethylene glycols. *Pharm Acta Helv.* 1975; 50:10–17. [PubMed: 234621]
6. Donbrow M, Azaz E, Pillersdorf A. Autoxidation of polysorbates. *J Pharm Sci.* 1978; 67:1676–1681. [PubMed: 31449]
7. Puz MJ, Johnson BA, Murphy BJ. Use of the antioxidant BHT in asymmetric membrane tablet coatings to stabilize the core to the acid catalyzed peroxide oxidation of a thioether drug. *Pharm Dev Technol.* 2005; 10:115–125. [PubMed: 15776819]
8. Hartauer KJ, Arbuthnot GN, Baertschi SW, Johnson RA, Luke WD, Pearson NG, Rickard EC, Tingle CA, Tsang PKS, Wiens RE. Influence of peroxide impurities in povidone and crospovidone on the stability of raloxifene hydrochloride in tablets: Identification and control of an oxidative degradation product. *Pharm Dev Technol.* 2000; 5:303–310. [PubMed: 10934729]
9. Akers MJ. Antioxidants in pharmaceutical products. *J Parenter Sci Technol.* 1982; 36:222–228. [PubMed: 6927751]

10. Hovorka SW, Schoneich C. Oxidative degradation of pharmaceuticals: Theory, mechanism and inhibition. *J Pharm Sci.* 2001; 90:253–269. [PubMed: 11170019]
11. Waterman KC, Adami RC, Alsante KM, Hong J, Landis MS, Lombardo F, Roberts CJ. Stabilization of pharmaceuticals to oxidative degradation. *Pharm Dev Technol.* 2002; 7:1–32. [PubMed: 11852692]
12. Munjal M, Repka MA. Improving stability of amorphous tetrahydrocannabinol in polymeric systems. *AAPS J.* 2004; 6(S1) Abstract R6086.
13. McGinity JW, Hill JA, La Via AL. Influence of peroxide impurities in polyethylene glycol on drug stability. *J Pharm Sci.* 1975; 64:356–357. [PubMed: 1127599]
14. Connors, KA.; Amidon, GL.; Stella, VJ. Chemical stability of pharmaceuticals: A handbook for pharmacists. 2nd ed.. John Wiley & Sons; New York: 1986.
15. Johnson, DM.; Gu, LC. Encyclopedia of pharmaceutical technology. 1st ed.. Marcel Dekker; New York: 1988. p. 415-449.
16. Johnson DM, Taylor WF. Degradation of fenoprostalene in polyethylene glycol 400. *J Pharm Sci.* 1984; 73:1414–1417. [PubMed: 6502492]
17. Wan LS, Hwang CL. Studies on the effect of gallate on the oxidation of aldehydes dispersed in cetomacrogol solutions. *J Pharm Sci.* 1969; 58:262–264. [PubMed: 5779878]
18. Kurechi T, Kato T. *Chem Pharm Bull.* 1982; 30:2964–2970.
19. Byrn, SR.; Pfeiffer, RR.; Stowell, JG. Solid-state chemistry of drugs. 2nd ed.. SSCI; West Lafayette: 1999.
20. Flora KP, Cradock JC, Davignon JP. Determination of delta-9-tetrahydrocannabinol in pharmaceutical vehicles by high-performance liquid chromatography. *J Chromatogr.* 1980; 206:117–123. [PubMed: 6260828]
21. Del Nobile MA, Mensitieri G, Manfredi C, Arpaia A, Nicolais L. Low molecular weight molecules diffusion in advanced polymers for food packaging applications. *Polym Adv Technol.* 1996; 7:409–417.
22. Del Nobile MA, Mensitieri G, Nicolais L. Effect of chemical composition on gas transport properties of ethylene-based ionomers. *Polym Int.* 1996; 41:73–78.
23. Chacko A, Mathew B. Influence of the nature of crosslinking agent on the oxidation behavior of crosslinked polystyrene-supported polyoxyethylene bound permanganate. *J Macromol Sci.* 2003; A40:1035–1056.
24. Ramaratnam, K.; Luo, J.; Luzinov, I. Morphology and wettability of ultrathin porous polymer films.. Abstracts of Papers, 229th ACS National Meeting; 2005.
25. Badawy SIF, Williams RC, Gilbert DL. Effect of different acids on solid-state stability of an ester prodrug of a IIb/IIIa glycoprotein receptor antagonist. *Pharm Dev Technol.* 1999; 4:325–331. [PubMed: 10434278]
26. Badawy SIF, Williams RC, Gilbert DL. Chemical stability of an ester prodrug of a glyco-protein IIb/IIIa receptor antagonist in solid dosage forms. *J Pharm Sci.* 1999; 88:428–433. [PubMed: 10187753]
27. van Drooge DJ, Hinrichs WLJ, Wegman KAM, Visser MR, Eissens AC, Frijlink HW. Solid dispersions based on inulin for the stabilization and formulation of D9-tetrahydrocannabinol. *Eur J Pharm Sci.* 2004; 21:511–518. [PubMed: 14998582]

Figure 1.
Chemical structures of THC and its primary thermo-oxidative degradation product, CBN.

Figure 2. Schematic of the studies conducted to identify the source and mechanism of oxidation of THC in PEO-VES polymeric systems.

Figure 3. Schematic of the study undertaken to examine the effect of processing and storage environment (effect of cross-linking) on the oxidative degradation of THC in PEO-VES patches. For example, Patch I was processed and stored in air, while Patch II was processed under nitrogen flow and stored in air.

Figure 4.

Effect of processing and storage environment (effect of cross-linking) on degradation of THC in PEO-VES patches prepared at 120°C and stored at 40°C for 2 months. I–IV refer to the patches as depicted in Figure 3 (n=3).

Figure 5. Stability of THC in pH-adjusted PEO-VES patches stored at 40°C, after 2 months. (NCD is the basic constituent—sodium citrate dihydrate). The patches were prepared by heating the formulations at 120°C (n=3).

Figure 6. Chemical stability and moisture adsorption of the PEO matrices prepared at 120°C and stored for 1 month at (a) 40°C/0% RH, and (b) 40°C/75% RH (n=2).

Table 1

Stability of THC in 80:20 Excipient:Drug Mixtures Stored at 40°C

Excipient	THC % Degraded Upon Storage at 40°C	
	1 Month	2 Months
CPG	9.6	20.7
PEG	3.2	4.8
VES	48.1	—
PEO	3.2	8.4
Pure THC	74.3	99.8

Table 2

Stability of THC in Presence of Increasing Proportions of PEO and VES

Mixture	THC % Degraded Upon Storage at 40°C	
	1 Month	2 Months
PEO:THC		
80:20	3.2 ± 0.3	8.4 ± 0.9
90:10	1.4 ± 0.3	3.4 ± 1.3
96:4	0.6 ± 0.1	2.0 ± 0.0
VES:THC		
70:30	42.8	—
80:20	48.1	—
90:10	55.1	—

Binary mixtures were prepared by heating at 120°C for 2–3 min (n = 3).

Table 3

Stability of THC in PEO-VES Matrices Containing Various Classes and Types of Antioxidants

PEO-VES-THC-Antioxidant Patches			
THC % Degradation Upon Storage at 40°C			
Antioxidant	% Antioxidant	1 Month	2 Months
BHT	0.20	12.1 ± 0.2	26.2 ± 6.1
BHT	2.00	10.7 ± 0.7	24.8 ± 3.9
BHA	2.00	12.6 ± 0.8	28.4 ± 1.0
Propyl Gallate	2.00	25.4 ± 9.5	54.2 ± 19.6
Ascorbic Acid	2.00	3.0 ± 0.5	5.8 ± 1.3
EDTA	0.05	12.9 ± 1.5	29.0 ± 2.9
FeSO ₄	0.03	12.9 ± 1.0	30.3 ± 0.5
None (Control)	0.00	13.0 ± 0.9	31.6 ± 3.6
Pure THC	0.00	74.3 ± 5.7	99.8

The matrices were processed at 120°C and stored at 40°C (n = 3).

Table 4

Apparent pH Values of the Polymer Patch Formulations (Without THC)

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

The patch was allowed to swell and form a gel by sonicating in presence of water. The pH values of the gel were recorded.