Polymeric Systems for Amorphous Δ^9-Tetrahydrocannabinol Produced by a Hot-Melt Method. Part I: Chemical and Thermal Stability during Processing

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ABSTRACT: The objective of the present research was to investigate the stability of an amorphous drug, Δ^9-tetrahydrocannabinol (THC) in polymer-based transmucosal systems. THC was incorporated in polyethylene oxide and hydroxypropylcellulose matrices by a hot-melt fabrication procedure, utilizing various processing aids. The chemical stability of the drug in the polymeric matrices was investigated with respect to processing temperature, processing time, formulation additives, and storage conditions. HPLC analysis of the THC-loaded systems indicated that the extent of drug degradation was influenced by all of the above mentioned variables. THC was particularly unstable in the vitamin E succinate-processed films, indicating a potential incompatibility. Thermal stability of the drug, polymers, and other ingredients at the elevated processing temperatures during the fabrication procedure, was evaluated using the isothermal mode of thermo-gravimetric analysis. When held at 160 and 200°C, the weight percentage of THC decreased linearly as a function of time. Weight loss was controlled by blending the drug with polymers, PEO and HPC, of which PEO was determined to be more effective. Although higher temperatures lowered the polymer melt viscosity, THC and other materials were chemically and thermally unstable at such high temperatures. Due to this, matrix fabrication was found to be favorable at relatively lower temperatures, such as 120°C. J Pharm Sci 95:1841–1853, 2006

Keywords: Δ^9-tetrahydrocannabinol; cannabinol; hot-melt; thermal analysis; isothermal stability; polymer; processing conditions; amorphous; polyethylene oxide; excipients; processing aids

INTRODUCTION

Δ^9-Tetrahydrocannabinol (THC) is one of the 66 cannabinoids present in *Cannabis sativa*,[1] and is the main source of the pharmacological effects caused by its consumption. THC is a brown, oily resin that is viscous and sticky at ambient conditions and hardens upon refrigeration, suggesting that the glass transition temperature (T_g) is below 25°C, necessitating its storage at relatively low temperatures for stability purposes. Indeed, T_g of the drug was well below room temperature as determined by van Drooge et al.[2] The stability of THC has been a subject of numerous investigations[3–12] and it has been reported that the drug is susceptible to decomposition by light, heat, and oxidation. Storage leads to a cumulative decrease in THC content

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through its oxidation to cannabinol (CBN), which is the most widely recognized thermo-oxidative degradation product of THC. However, other degradation products may also be formed besides CBN. The issue of stability was perceived to be a significant one, when the authors observed that more than 80% of the pure THC was lost within 1 month at 25°C and 0% relative humidity (unpublished results). Thus, one of the most important aspects for the formulation of THC dosage forms is to overcome this stability problem.

Although cannabis has been used for medicinal purposes since centuries, its therapeutic potential was recognized only recently when THC was marketed as an active ingredient of Marinol®/ Dronabinol capsules. The product is indicated for its antiemetic and appetite stimulant properties in cancer chemotherapy and AIDS, respectively. Due to the poor solubility and significant first-pass metabolism, the oral absorption of THC is slow and erratic, resulting in low bioavailability. In view of this, several other routes have been investigated to improve the bioavailability of THC, namely pulmonary,[13] ophthalmic,[14] sublingual,[15] rectal,[16,17] and transdermal.[18] While each of these delivery routes have their associated advantages and disadvantages, the intra-oral transmucosal or buccal route of drug administration has some unique benefits, including avoiding the first-pass effect, being easily accessible and enhancing patient compliance. Buccal drug delivery could provide a rapid onset of action in addition to the controlled release of THC. Currently, cannabis-based medicines are administered as a sublingual spray, which give adequate therapeutic results, but an alternative solid dosage form would confer advantages in patient compliance and higher potential doses. However, the stability of such formulations must be high.

The unique physico-chemical properties, tarlike nature and low stability of THC pose significant challenges during formulation development, in addition to playing critical role in the bioavailability of the drug. Most of the research related to the formulation of THC is aimed towards evaluation of the pharmacological properties of the drug. Studies that investigated the stability aspect of THC have mainly focused on the drug decomposition in plant extracts. However, to achieve the desired therapeutic benefits of THC in humans more attention needs to be directed towards formulating a stable drug delivery system.

Due to the drug delivery problems associated with THC, formulation studies were initiated to develop a new dosage form suitable for buccal administration to humans. A flexible polymeric matrix system that adheres to the buccal mucosa for a predetermined period of time acts as the ideal drug carrier for oral transmucosal delivery. This matrix system can be fabricated from the polymer formulations with the drug, utilizing solid-melt (hot-melt casting or hot-melt extrusion) or solvent-cast methods.

An objective of the present study was to incorporate THC in to flexible polymeric matrix systems utilizing hot-melt casting methods. The research was focused on the stabilization of THC and the investigation of various parameters that influence its stability, such as processing time and temperature. The effects of different types of plasticizers and processing aids on the chemical stability of the films, exposed to different storage conditions, were also examined. The thermal stability of THC and other formulation components, at the elevated processing temperatures, was studied using the isothermal mode of thermogravimetric analysis (TGA). An understanding of the thermal properties of the drug will be useful in modulating the process parameters for successful development of stable dosage forms containing THC or its pro-drugs. These systems may be utilized for systemic delivery of the drug via sublingual, buccal, or other alternative routes.

EXPERIMENTAL

Materials

The following chemicals were used as obtained: Miglyol 812, 829, and 840 (Sasol, Witten, Germany GmbH); Capmul PG-8, PG-12, MCM, and Captex 200 and 355 (Abitec Corp., Janesville, WI); Labrasol and Labrafil (Gattefosse, France); Triethanolamine (Fisher, Fairlawn, NJ); PEG-400, glyceryl monostearate, isopropyl myristate, diethyl phthalate, ethyl oleate, vitamin E succinate, almond oil, castor oil, light mineral oil, petrolatum, and butylhydroxy toluene (Spectrum Chemical, Inc., New Brunswick, NJ); Tween 80 (Uniqema, Wilmington, DE); Polyethylene Oxide—N10 (Sigma-Aldrich, 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