International Journal of Pharmaceutics 362 (2008) 126–132

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Chemical stability and bioadhesive properties of an ester prodrug of Δ^9-tetrahydrocannabinol in poly(ethylene oxide) matrices: Effect of formulation additives

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ARTICLE INFO

Article history:
Received 23 April 2008
Received in revised form 21 June 2008
Accepted 24 June 2008
Available online 5 July 2008

Keywords:
Bioadhesion
THC
Poly(ethylene oxide)
Stability
Prodrug
Antioxidants

ABSTRACT

The objective of the present research was to stabilize a novel hemiglutarate ester prodrug of Δ^9-tetrahydrocannabinol (THC), in polyethylene oxide (PEO) polymeric matrices produced by hot-melt fabrication, for systemic delivery of THC through the oral transmucosal route. For this purpose, the influence of pH modifiers and antioxidants employed as stabilizing agents in these matrices was investigated. Based on the stability studies, two final formulations were made, and the stability of the active was assessed in these systems. In addition, the bioadhesive properties of PEO matrices were studied as a function of bioadhesive polymer type and concentration, contact time, drug loading and wetting time. Of all of the polymers investigated, bioadhesion was highest with Carbopol® 971p. Bioadhesion increased with bioadhesive polymer concentration and wetting time to a certain level beyond which there was no further contribution. Both the contact time and drug loading influenced the bioadhesion. Severe degradation of the prodrug was observed during storage, even at room temperature (75% at the end of 3 months). Incorporation of the stabilizing agents in the PEO matrices reduced the degradation of the prodrug considerably. Citric acid was the most effective of all of the pH modifiers studied. Among the various antioxidants utilized, degradation was observed least in presence of BHT and ascorbic acid. Only 7.6% and 8.2% of prodrug degraded in these matrices, respectively, as compared to the PEO-only matrices (59.4%) at the end of 3 months at 25 °C/60% RH. The prodrug was very stable in both of the final formulations at the end of the 3 months at 40 °C/75% RH.

1. Introduction

Δ^9-Tetrahydrocannabinol (THC), the major pharmacologically active constituent of *Cannabis sativa* exhibits therapeutic potential in the treatment of nausea and vomiting during cancer chemotherapy, anorexia associated with weight loss in AIDS patients, glaucoma, analgesia, anxiety as well as other potential indications (Voth and Schwartz, 1997). Despite the promising clinical potential of THC, an effective dosage form has not been developed to date. The only commercially available dosage form with a constant THC content is the soft gelatin capsule for oral administration, marketed in the USA as Marinol®. In this formulation, however, the drug has limited stability and therefore has to be stored at low temperatures (4 °C). Moreover, the oral bioavailability of the drug is low (~6%) and inconsistent, which is mainly due to its high first-pass metabolism and poor solubility (Ohlsson et al., 1980). In addition to the pharmacokinetic limitations, the physicochemical properties of THC present a major challenge in the development of a suitable dosage form. THC is a poorly water-soluble, amorphous substance which is sticky, resin-like and highly viscous, which makes it difficult to handle and process. Furthermore, the instability of THC, especially in acidic solutions, and when exposed to heat, air and light has been reported by various researchers (Mechoulam, 1970; Fairbairn et al., 1976).

THC-hemiglutarate (THC-HG), a prodrug of THC, has been developed in an attempt to overcome the pharmacokinetic limitations and improve the physicochemical properties of the parent drug. The structure of THC-HG is depicted in Fig. 1. Due to the significant

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doi:10.1016/j.ijpharm.2008.06.025

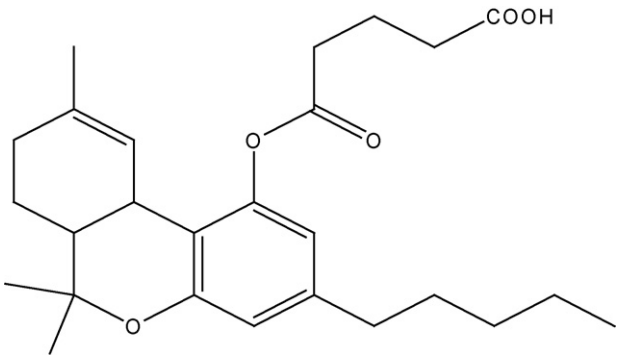

Fig. 1. Chemical structure of THC-HG.

limitations associated with traditional routes of administration, several non-parenteral routes have also been explored for systemic delivery of THC. These include sublingual (Guy and Flint, 2000), rectal (ElSohly et al., 1991), nasal (Harris et al., 1988) and transdermal (Challapalli and Stinchcomb, 2002). With each of these routes having their own disadvantages, an attempt has been made to systemically deliver THC in the form of its novel prodrug, THC-HG through the oral transmucosal route, since it offers distinct advantages including avoidance of first-pass effect, easy accessibility and enhanced patient compliance. The oral mucosa is relatively permeable with a rich blood supply, robust and shows short recovery times after stress or damage. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery (Shojaei, 1998).

A major disadvantage of oral mucosal delivery, however, is the lack of retention of the dosage form at the intended site for a desirable duration and hence drug loss due to salivary wash out, involuntary tongue movements and swallowing. Consequently, oral mucosal delivery requires the use of mucoadhesive polymers to overcome these limitations. The mucoadhesives increase residence time at the absorption site, improve contact between the delivery system and the absorption site, and provide localization to specified oral mucosa regions to enhance bioavailability. The interaction between the mucus and mucoadhesive polymers has been thought to be a two-stage process (Wu, 1982). In the first stage known as the contact stage, the wetting of the mucoadhesive polymer upon contact with a mucosal membrane leads to swelling of the polymer followed by disentanglement and interpenetration of polymer and mucus chains. The second stage known as the consolidation stage, then involves the formation of interfacial bonds between the interpenetrated chains leading to prolonged adhesion. These bonds are of secondary type, such as electrostatic forces, van der Waals forces, hydrogen bonds and hydrophobic interactions and are relatively weak (Solomonidou et al., 2001). Physical properties of the mucoadhesive such as chemical structure, molecular weight, rate of hydration and polymer concentration can have a major impact on their mucoadhesion and consequently their eventual duration of retention (Smart, 1991). Hence, for successful delivery of THC-HG across the oral mucosa, a bioadhesion assessment in the presence of potential bioadhesive polymers is imperative.

A survey of the scientific literature indicates that there are only few references on prodrugs of THC (all of them on THC-hemisuccinate) that have focused on studying the stability and bioavailability of the drug in various dosage forms (ElSohly et al., 1991; Munjal et al., 2006). However, no research has been focused to investigate the physicochemical properties or stability of the novel hemiglutarate prodrug in any of the dosage forms to date. Preformulation studies conducted by our research group revealed that THC-HG is highly unstable even when stored at 4 °C due to a low glass transition temperature (0.586 °C). pH stability studies revealed the instability of the prodrug in an aqueous environment. Furthermore, THC-HG was found to be sensitive in the presence of oxygen and exhibited significant degradation under elevated relative humidity conditions (Thumma et al., in press). In the present study, an attempt has therefore been made to stabilize the prodrug via incorporation into PEO polymeric matrices produced by a hot-melt method. The influence of pH modifiers and antioxidants employed as stabilizing agents in these matrices was investigated. In addition, since optimal bioadhesion is essential for the successful application of an oral transmucosal matrix system, the bioadhesive performance of the active-incorporated PEO matrices in the presence of various potential mucoadhesive polymers was also assessed.

2. Materials and methods

2.1. Materials

PEO [PolyOx® WSR N-80 (PEO N-80), MW 200,000 Da] and hydroxypropylmethyl cellulose (Methocel® K4M) (HPMC) were kindly donated by Dow Chemical Company (Midland, MI) and hydroxylpropyl cellulose (HPC) (Klucel® LF) by Aqualon Division, Hercules, Inc. (Wilmington, DE). Vitamin E succinate (VES), sodium carboxymethylcellulose (SCMC), fumaric acid, citric acid anhydrous, monobasic sodium phosphate, tartaric acid, succinic acid, sodium citrate dihydrate, sodium tartarate, BHT, BHA, ascorbic acid, propyl gallate, EDTA and sodium dodecyl sulfate (SLS) were purchased from Spectrum Chemical, Inc. (Gardena, CA). Methanol and acetonitrile (both HPLC grade) were obtained from Fischer Chemicals (Fair Lawn, NJ). Carbopol® 971p and polycarbophil (Noveon® AA-1) were purchased from Noveon, Inc. (Cleveland, OH). Chitosan was procured from Sigma–Aldrich (St. Louis, MO) and glacial acetic acid from J.T. Baker (Phillipsburg, NJ).

2.2. Preparation of polymeric matrices by hot-melt method

Polymeric matrices incorporating THC-HG at 5% (w/w) were made utilizing a hot-melt method. Briefly, a die containing a 13-mm diameter opening was placed on top of a brass sheet and heated at 110 °C. Approximately 200 mg of the physical mixture of drug, polymer and other excipients was positioned in the orifice of the die, and compressed using a punch. This compressed mixture was heated for 5–10 min to form a melt, followed by cooling under room conditions to form a thin polymeric patch. Patch thickness ranged from 1.1 to 1.3 mm. The diameter of the patches produced was approximately 12.9 ± 0.2 mm. PEO N-80 grade (molecular weight, 200,000) was used as the matrix polymer for all of the studies, unless otherwise stated.

2.3. Bioadhesion studies

Bioadhesive measurements were performed on the PEO polymeric matrices utilizing a TA.XT2i Texture Analyzer (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK) equipped with Texture Expert™ software. Porcine buccal mucosa was used as a biological substrate. The samples ($n = 5$) were wetted with artificial saliva (Prodduturi et al., 2005) (adjusted to a pH of 6.8 ± 0.05) for approximately 60 s and placed on the lower base of the instrument. The mucosal substrate was attached to the probe with a cyano-acrylate adhesive and equilibrated with the artificial saliva before the bioadhesion testing. The probe lined with mucosa was set to approach the sample with a predetermined speed of 0.5 mm/s and applied a force of 3.5 N. The test speed was 0.1 mm/s. The probe was then withdrawn at a