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CONTROLLED RELEASE TABLET FORMULATION CONTAINING NATURAL ⁹ TETRAHYDROCANNABINOL

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Abstract

Cannabinoids are increasingly being used in the treatment of chemotherapy induced nausea and vomiting (CINV) because of their action on the cannabinoid receptors, CB1 and CB2. The currently marketed capsule formulations (sesame oil based and crystalline powder) are required to be administered frequently to maintain therapeutic levels, which leads to non-compliance. In the present study, oral controlled release tablet formulations of ⁹-tetrahydrocannabinol (THC) were prepared using the lipids Precirol[®] and Compritol[®]. Release profiles using THC-lipid matrices and/or with the lipids in the external phase (blend) were evaluated. The effect of directly compressible diluents lactose mixture (Ludipress[®]), dicalcium phosphate anhydrous (Emcompress[®]) and microcrystalline cellulose (Avicel[®] 102) on tablet characteristics and *in vitro* drug release was also investigated. Further, *in vitro* THC release in the presence of a lipase inhibitor, Pluronic[®] F68, was also studied. A 24 h zero order THC release profile was obtained with a combination of Precirol[®] and Compritol[®] in the compression blend. Addition of Pluronic[®] F68 did not alter THC release *in vitro*. These optimized tablets were chemically and physically stable for 3 months, the last time point tested, at 25°C/60% RH. The overall results demonstrate the feasibility of preparing oral THC tablets for once a day administration which can improve CINV management.

Keywords

Cannabinoids; ⁹-tetrahydrocannabinol; oral; Tablets; Precirol[®]; Compritol[®]

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Declaration of conflicts of interest

The authors report no conflicts of interest in this work.

Introduction

Chemotherapy Induced Nausea and Vomiting (CINV) is the most common and feared post chemotherapy side-effect¹⁻⁷. Around 30 to 90% of patients undergoing chemotherapy experience this, thereby reducing the quality of life (QOL)⁷. One of the classes of anti-emetics used for this purpose are the cannabinoids. Tetrahydrocannabinol (THC), a component of cannabis has anti-CINV effects. THC binds to the cannabinoid receptors, thereby controlling vomiting and is also beneficial in the treatment of weight loss⁷⁻¹⁴. Commercially available pharmaceutical cannabinoids include Nabilone (Cesamet[®]) and Dronabinol (Marinol[®])¹⁵⁻¹⁷. Synthetic THC used in Dronabinol as well as the natural THC obtained from the plant, is a resinous sticky oil that hardens on refrigeration. THC undergoes degradation through several mechanisms¹⁸⁻²⁰ and handling of the resinous form is very difficult from a formulation point of view. Dronabinol is thus formulated as a sesame oil solution of THC and is supplied in a soft-gelatin capsule. Nabilone, on the other hand, is a synthetic THC derivative that is crystalline in nature and is thus filled into a hard gelatin capsule. Nabilone is given twice a day orally up to 48 hours post chemotherapy¹⁵ and Dronabinol, every 2-4 hours orally for a total of 4-6 doses a day^{16, 17}, a frequent reason for patient noncompliance issues. Also, use of Dronabinol is contraindicated in case of patients with hypersensitivity reaction to sesame oil^{16, 17}.

The goal of this research project was to develop a sustained release oral tablet formulation using naturally occurring THC.

To overcome the challenges in handling the oily resinous characteristics of THC, a lipid based formulation approach was selected to develop controlled release THC tablets^{21, 22}.

In vivo, it has been shown that THC undergoes high first pass metabolism, transforming it into its 11-hydroxy metabolite, which results in very low oral bioavailability^{19, 23, 24}. A controlled release formulation could maintain a low but effective level of THC in the plasma which could in turn reduce the concentration of the 11-hydroxy metabolite in the plasma, reducing the psychological side-effects. Additionally, presence of a lipid matrix might promote lymphatic uptake and increase bioavailability.²² Also, to our knowledge this is the first attempt at producing a sustained release tablet dosage form for THC.

The instability of THC in solid state has been a major obstacle previously^{18, 25}. THC is an amorphous drug and therefore does not possess a definite crystal lattice structure and is thus more susceptible to oxidative degradation into its metabolite cannabitol (CBN). Use of excipients such as cross linking and barrier forming polymers can be one way of controlling this, as there will be less space in the matrix for atmospheric air diffusion¹⁸. The active moiety is thus protected. In this study, we have used Compritol in the formulation. This lipid has been reported to form protective barriers, thus increasing stability on storage²⁶. Also it has a very low peroxide value of 6 meq O₂/Kg indicating high stability which is also an important aspect considering the nature of THC. This indicates that the lipid is not easily oxidized, shielding the active ingredient from atmospheric oxidation²⁶. This is an added advantage of using the lipid matrix, which may help mitigate this issue. The other lipid used in this formulation is Precirol. This lipid has a high plasticity thereby giving it a high

resistance to fracture, which makes it very useful in tablets made via direct compression. Commercially, both Compritol and Precirol are available as fine white powders with a particle size of less than 50 μ M. Both lipids have a melting point of less than 70°C which is important considering the thermo-labile nature of THC. Also, it has been shown previously that the lipids are stable at these temperatures. There have also been multiple studies with these lipids in producing sustained release and taste masked dosage forms via direct compression²⁶⁻³¹. Additionally, Compritol is a barrier forming lipid which helps it shield sensitive APIs²⁶. Also, both the lipids have lubricating properties which would help in blending and compression.

Materials and methods

Precirol[®] ATO 5 (Glycerol Distearate) and Compritol[®] 888 ATO (Glycerol Dibehenate) were obtained as gift samples from Gatefosse (St.Priest, France), Avicel[®] 102 (Micro-crystalline Cellulose) was obtained from FMC Biopolymer (Philadelphia, PA), Emcompress[®] (Dicalcium Phosphate Anhydrous, DCPA), from JRS Pharma (Rosenberg, Germany), Ludipress[®] (composed of Lactose monohydrate, Povidone K30 (Kollidon[®] 30) and Crospovidone (Kollidon[®] CL) from BASF Fine chemicals (Switzerland), Pluronic[®] F68 from Sigma Aldrich (St. Louis, Missouri), Aerosil[®] R972 from Evonik Industries (Germany), Magnesium Stearate (Mg. Stearate) from Spectrum Chemicals (Gardena, CA). All solvents used for analysis were of analytical grade.

Methods

Three types of THC containing tablets were prepared. The variations involved the use of the lipid component either in the lipid-THC matrix, lipid in external phase (added during the blending phase) or incorporating lipid in the matrix as well as in the blend stage. The various formulations evaluated are shown in Tables 1 & 2.

Preparation of lipid-drug matrix

The lipid-drug matrices were prepared by solid dispersion technique. THC lipid dispersions, 25% w/w, were made by heating the mixture to 70°C, through which the drug was dispersed in the lipid, followed by molding of the dispersion into slugs using 1 mL tuberculin syringes. The matrix was cryo-milled using a Fitz Mill L1A (The Fitzpatrick Company, Elmhurst, Illinois) and sieved through ASTM sieve # 70 (mesh opening of 210 microns) to maintain a particle size of less than 200 μ M.

Preparation of tablets

Granules were compressed using a Manual Tablet Compaction Machine, MTCM-I (Globe Pharma Inc., New Brunswick, NJ) with 8mm flat faced punches at compression forces ranging from 7.6kN to 9.8kN. THC-lipid matrices were blended with the other excipients and directly compressed. In some formulations additional lipid was included during the blending stage also.

Alternatively, THC (in hexane) was coated on the filler (DPCA/ MCC/ Lactose), dried at 25°C, blended with the other excipients including the lipids under evaluation. The blend was directly compressed into tablets.

Both methods used in the tablet manufacture use processing temperatures that are well below the degradation temperature of THC. In the first method, the temperature for preparing the dispersion is well below the temperature at which THC degrades³². Also, the subsequent cryo-milling steps ensure low temperatures are maintained in the mill. In the second manufacturing method, THC is coated on to the filler and dried at 25°C, so thermal degradation is not an issue in this case.

Evaluation of tablets

Physical characteristics—The physical properties of the tablets such as appearance, texture, hardness, weight variation, friability were determined in accordance to standard protocols. Hardness was determined using VK-200 tablet hardness tester (Varian Inc, NC).

Assay and Content uniformity of tablets—About 5 tablets separately were powdered in a mortar and pestle; about 2 mg of the powder was accurately weighed and extracted in 1mL of methanol, followed by centrifugation (13000 rpm, 20 min). The supernatant was collected and diluted suitably with mobile phase and was analyzed in triplicate by HPLC using the analytical method described in the section below.

Analytical method—A Waters HPLC system (Mildford, Massachusetts) consisting of Waters 600 pump controller, refrigerated Waters 717 plus autosampler, Waters 2487 UV detector, and Agilent (Santa Clara, California) 3395 integrator was used in the present investigation. Initial stock solution (1mg/mL) of THC was prepared in ethanol and stored at -20° C till used. Standards were prepared by pipetting out a known amount of stock solution and evaporating it under a stream of nitrogen gas. Suitable standards were prepared by reconstitution in the mobile phase. A Luna PFP (2), 4.6 × 250mm column, Phenomenex (Torrance, CA) was used for the separation and analytical purposes. Mobile phase had a mixture of methanol – water [containing 0.84% (v/v) glacial acetic acid] in 85:15 ratios. The detector was set at an analytical wavelength of 226nm, while the injection volume was 20uL. The standards were prepared in the concentration range of 1–100 µg/mL. The standard calibration curve was derived and the parameters such as regression coefficient (r^2), slope and Y- intercept were noted to establish the linearity of the method. Response after repeated injections from the same sample was recorded to check for precision and dissolution medium with the placebo formulations were injected to ensure there was no interference. The method was also validated with respect to limit of detection (3 times signal-to-noise ratio) and limit of quantification (10 times signal-to-noise ratio).

In vitro drug release studies—The *in vitro* drug release (dissolution) studies were performed using USP type I (basket) and type II (paddle) apparatus at 100 rpm and 50 rpm, respectively, and THC release from the tablets was evaluated. The dissolution medium consisted of 900 mL of water containing sodium lauryl sulfate (SLS) (0.5 %w/v), while the temperature was maintained at 37°C±0.5°C. At predetermined time intervals, samples (1

mL) were withdrawn and replaced with an equal volume of dissolution media. The samples were then analyzed by HPLC.

Stability studies—Stability studies were performed as per the ICH guidelines. The tablets were packed into small aluminum pouches which were then sealed under nitrogen. The samples were loaded into stability chambers maintained at $25\pm 2^{\circ}\text{C}/60\pm 5\%$ RH and $40\pm 2^{\circ}\text{C}/75\pm 5\%$ RH. At predetermined time points, samples were withdrawn for evaluation.

Results and Discussions

Formulations

A total of 14 formulations with varying excipient proportions were prepared. Qualitative and quantitative composition of all formulations are listed in Tables 1 & 2.

Analytical method

The analytical method showed linearity within the range $0.5 - 100\ \mu\text{g/mL}$, with an r^2 value of 0.99. Limit of detection and limit of quantification were found to be $10\ \text{ng/mL}$ and $30\ \text{ng/mL}$, respectively, and the retention time for THC was about 11.2 min. The method was observed to be specific and precise.

Evaluation of the tablets

Assay, Content uniformity and Physical characteristics—THC assay ranged between 96 to 102%, demonstrating process stability. Content uniformity of all the formulations was within acceptable limits with the RSD of the individual tablet contents falling within 6% of the mean (Table 3). The target tablet weight and hardness were 200 mg and 5.4 kp, respectively. Weight variation ($200\pm 2\ \text{mg}$), friability and thickness were all observed to be within limits. Tablet hardness was found to range between 5.3 – 5.6kp ($n=3$) over the entire range of formulations (Table 3).

In vitro drug release studies—Release of THC from the formulations was seen to be influenced by the type of filler (DCPA/MCC/Lactose) used in the formulation, as shown in Figure 1. In the case of MCC (Avicel) as the filler (F-2), the drug release was more uneven with about 70 % THC being released within 1h, followed by minimal release at further time points. Additionally, ‘tablet splitting’ was observed in the dissolution media in these formulations (F-2). Although hardness was kept similar in all three formulations, this phenomenon was seen only in formulation F-2.

Tablets prepared using lactose as the filler (F-3), showed good physical characteristics, but a release of 55% in 1h and 78% in 6 h was observed. On the other hand, tablets with DCPA as the filler (F-1) released about 34% in 1h and about 74% by the end of 6 h. Moreover, the THC release profile from formulation F-1 was much smoother and more uniform compared to formulations F-2 and F-3. On the basis of these results, DCPA was selected as the filler for further studies.

The dissolution conditions recommended by FDA for the marketed THC formulations, Nabilone and Dronabinol, are shown in Table 4 ³³.

The currently marketed dosage forms are immediate release capsules. Thus, there was a need to develop a dissolution method to study THC release from the proposed controlled release formulations. Since THC release is known to be pH independent³⁴ and the dissolution medium was able to maintain sink conditions, apparatus type (basket or paddle) and rpm (50 or 100) were the only parameters that were varied.

As shown in Figure 2, THC release from F-1 was 41% and 52% at the end of 6 hours when a paddle was employed at 50 and 100 rpm, respectively. When an USP Type I Apparatus (basket) was used THC release was 48% and 76% in 6 hours at 50 and 100 rpm, respectively. The higher drug release in the basket apparatus, could be due to the greater erosion effect on the bottom layers of the tablets, due to abrasion.

In order to optimize the release characteristics of THC from the formulations, it was decided that the more stressful dissolution conditions (producing faster release rates) would be used since these formulations would be more rugged in nature. Considering this, the basket apparatus at 100 rpm was selected for studying the release characteristics of the formulations. Release profile with the paddle method at 100 rpm, as per the FDA approved method, will be determined on the formulation showing a sustained 24h release profile under the stress conditions.

As discussed earlier, F-1 released 76% of the THC in the formulation at the end of 6 hours (Fig. 2), when a basket at 100 rpm was employed. In order to slow down the release, formulation F-4 was prepared using 20 mg of additional Precirol® in the blend phase (on top of the 30 mg in the lipid matrix). The tablet weight was kept at 200 mg by adjusting the amount of DCPA. Another formulation, F-5, was prepared with the total amount of lipid added externally in the blend phase. In this case, THC, dissolved in hexane, was coated onto DCPA and dried in an oven at 25°C for 30 minutes, before blending it with the other excipients. Formulation F-4, showed 51% THC release at the end of 6 hours with insignificant release at the later time points (Fig. 3). Formulation F-5 exhibited a much faster release profile with a t_{90} (time taken to release 90 % of drug) of less than 6 hours. From these results, it can be concluded that Precirol®, used internally in the drug-lipid matrix or externally in the blend phase significantly diminished drug release, but the inclusion of the lipid in the internal phase had a greater sustained release effect. On the other hand, when Compritol® was used in the lipid matrix (F-8), the release was found to be very erratic. From the data (not shown), it was evident that the drug was being released in uneven bursts. Erratic release in the presence of compritol in the matrix could be attributed to the comparatively higher lipophilicity of compritol. Compritol is a C-22 chain lipid and THC would have higher affinity for the lipid. Therefore, the diffusion and release from this matrix was not smooth and uniform. Also, irrespective of the lipid used, all the tablets eroded slowly as the study progressed.

In view of the relative rapid and uniform release profile of THC from formulation F-5, the matrix phase was not studied any further and all subsequent formulations were prepared with the lipid added directly to the blend and with THC coated onto the filler. The lipid content in the external phase was increased to 60 mg per tablet in formulation F-6. As can be seen from Figure 4, 83% THC release was observed in 10 hours.

In vivo, one of the major factors that could significantly affect the release profile of the drug from a lipid based tablet is lipolysis. The lipases present in the GIT digest the lipids rapidly, thereby causing rapid drug release. An approach to counter the effect of these enzymes is to use long chain lipids³⁵ and stabilizers³⁶. Stabilizers act by inhibiting the degradation of drugs through lipolysis. Pluronic® F68, a triblock polymer, acts by blocking the activity of co-lipase enzyme. For lipolysis, the particle surface needs to have a lipase anchored to it with co-lipase playing an important role in facilitating the activity of lipase on the lipid surface. One of the predominant mechanism of co-lipase is to anchor the lipase to the particle surface and other is to prevent the inactivation of lipase by the action by bile salts³⁶. A stabilizer reduces the adsorption of lipases on the particle surface through a mechanism called the “windscreen wiper effect”³⁶ wherein the lipases are prevented from anchorage and thus blocking the initial necessary step for degradation of lipid³⁷. Several studies have shown that use of Pluronic® F68, as a stabilizer has been successful in preventing lipolysis *in vitro*³⁸. Also, the property of Pluronic® F68’s increased efficiency with increasing protein molecular weight, further facilitates the anti lipolytic activity, considering the high molecular weight of the lipases, which is approximately 50,000 kDa³⁷.

Based on this, formulation F-7 was prepared with Pluronic® F68, added as a stabilizer, to study the effect of its inclusion on the release of THC from F-6. It was seen that inclusion of Pluronic® F68 did not significantly affect THC release (Fig. 4; $f_2 = 77$).

Also, Compritol®, a C-22 chained ester of behenic acid, is impervious to emulsification, a step that is pre-requisite for lipolysis^{35, 39, 40}, and formulations based on Compritol® would likely show minimum change in release profiles as a result of enzymatic degradation of the lipids. Thus, formulations F-9 & F-10 were prepared substituting Compritol® in place of Precirol® in F-6 and F-7. Compritol® was added directly to the blend. These formulations, F-9 and F-10, showed a very slow release rate of 5% and 4%, respectively, at the end of 10 hours (Fig. 4).

The combined effect of Compritol® and Precirol® was then investigated (F-11, F-12, F-13 and F-14). Formulations F-12 & F-14 contained Pluronic® F68 in the composition. Figure 5 shows that 100% drug release was observed from all formulations. F-13 and F-14 had better release profiles compared to F-11 and F-12.

Effect of THC dose on the release profile—To simulate the effect of dose on percentage release, the release studies were also carried out using two tablets of formulation F-14 (containing 10 mg THC each) per jar. Though this does not mimic adding a single 20 mg THC tablet, the results would provide additional information with respect to the THC release profiles at higher THC doses (dose weight ratio formulations) and the performance of the dissolution medium (0.5% SLS in water). THC release profiles from the lower dose, 10 mg (single tablet), and higher dose, 20 mg (double tablet), formulations was observed to be similar. Similarity (f_2) factors were calculated and the f_2 value was 68, suggesting that the drug release profile remained significantly unchanged.

The dose effect dissolution study was done using the paddle apparatus, as suggested by the FDA for testing Dronabinol. About 100 % THC release was seen at 22 hours at a paddle

speed of 100 rpm from both the single and double doses (Fig. 6). These results suggest that doubling the dose to 20 mg in a dose-weight ratio based formulation would not affect the release profile.

Drug release model—The release profile obtained from formulation F-14 was fitted into various models like Zero order (r^2 adjusted = 0.99), First order (r^2 adjusted = 0.92), Higuchi diffusion kinetics (r^2 adjusted = 0.97), Korsemeyer Peppas (r^2 adjusted = 0.99), Hixon Crowel (r^2 adjusted = 0.96). Considering the fact that THC release from these tablets was through diffusion from an insoluble matrix, the Higuchi model of release would be most appropriate.

Stability studies—The stability study results demonstrated that formulation F-14 was physically and chemically stable at $25\pm 2^\circ\text{C}/60\pm 5\% \text{RH}$ for 3 months. About 7% drug loss however, was observed at $40\pm 2^\circ\text{C}/75\pm 5\% \text{RH}$ in the same time period. The thermolabile characteristics of THC and susceptibility to oxidation is probably responsible for this. The stability can be improved with the addition of antioxidants and an intermediate stress condition, $30\pm 2^\circ\text{C}/65\pm 5\% \text{RH}$, should probably be more applicable for stability testing.

Conclusions

This study demonstrates that THC can be successfully formulated into a controlled release tablet. With an optimal lipid combination and proportion, it is possible to tailor the drug release to meet the desired plasma concentration time profile. Also, dispersion of THC in melted lipids followed by cryo-milling or the coating of THC (in hexane) on DCPA followed by drying before blending and compression proved to be good methods for overcoming the handling issues. The use of Pluronic® F68 as a stabilizer against lipolysis did not alter the release profile *in vitro*. Further studies are being planned to establish the stabilizing activity of Pluronic® F68 and subsequent oral bioavailability, *in vivo*.

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References

1. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM, et al. On the receiving end--patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol*. 1983 Feb; 19(2):203–208. PubMed PMID: 6681766. Epub 1983/02/01. eng. [PubMed: 6681766]
2. Dibble SL, Casey K, Nussey B, Israel J, Luce J. Chemotherapy-induced vomiting in women treated for breast cancer. *Oncol Nurs Forum*. 2004 Jan-Feb;31(1):E1–E8. PubMed PMID: 14722600. Epub 2004/01/15. eng. [PubMed: 14722600]
3. Eckert RM. Understanding anticipatory nausea. *Oncol Nurs Forum*. 2001 Nov-Dec;28(10):1553–1558. quiz 9–60. PubMed PMID: 11759303. Epub 2002/01/05. eng. [PubMed: 11759303]
4. Griffin AM, Butow PN, Coates AS, Childs AM, Ellis PM, Dunn SM, et al. On the receiving end. V: Patient perceptions of the side effects of cancer chemotherapy in 1993. *Ann Oncol*. 1996 Feb; 7(2): 189–195. PubMed PMID: 8777177. Epub 1996/02/01. eng. [PubMed: 8777177]

5. Jordan K, Sippel C, Schmoll HJ. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. *Oncologist*. 2007 Sep; 12(9): 1143–1150. PubMed PMID: 17914084. Epub 2007/10/05. eng. [PubMed: 17914084]
6. Tipton JM, McDaniel RW, Barbour L, Johnston MP, Kayne M, LeRoy P, et al. Putting evidence into practice: evidence-based interventions to prevent, manage, and treat chemotherapy-induced nausea and vomiting. *Clin J Oncol Nurs*. 2007 Feb; 11(1):69–78. PubMed PMID: 17441398. Epub 2007/04/20. eng. [PubMed: 17441398]
7. Viale PH. Update on the management of chemotherapy-induced nausea and vomiting. *J Infus Nurs*. 2006 Sep-Oct;29(5):283–292. PubMed PMID: 17035890. Epub 2006/10/13. eng. [PubMed: 17035890]
8. Andrews PL, Naylor RJ, Joss RA. Neuropharmacology of emesis and its relevance to anti-emetic therapy. Consensus and controversies. *Support Care Cancer*. 1998 May; 6(3):197–203. PubMed PMID: 9629870. Epub 1998/06/18. eng. [PubMed: 9629870]
9. Bender CM, McDaniel RW, Murphy-Ende K, Pickett M, Rittenberg CN, Rogers MP, et al. Chemotherapy-induced nausea and vomiting. *Clin J Oncol Nurs*. 2002 Mar-Apr;6(2):94–102. PubMed PMID: 11889684. Epub 2002/03/14. eng. [PubMed: 11889684]
10. Faigel DO. A clinical approach to constipation. *Clin Cornerstone*. 2002; 4(4):11–21. PubMed PMID: 12739323. Epub 2003/05/13. eng. [PubMed: 12739323]
11. Hesketh PJ, Van Belle S, Aapro M, Tattersall FD, Naylor RJ, Hargreaves R, et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur J Cancer*. 2003 May; 39(8):1074–1080. PubMed PMID: 12736106. Epub 2003/05/09. eng. [PubMed: 12736106]
12. Kalant H. Medicinal use of cannabis: history and current status. *Pain Res Manag*. 2001 Summer; 6(2):80–91. PubMed PMID: 11854770. Epub 2002/02/21. eng. [PubMed: 11854770]
13. Shelke AR, Mustian KM, Morrow GR. The pathophysiology of treatment-related nausea and vomiting in cancer patients: current models. *Indian J Physiol Pharmacol*. 2004 Jul; 48(3):256–268. PubMed PMID: 15648398. Epub 2005/01/15. eng. [PubMed: 15648398]
14. Spencer Green ZN, Sarah Nordquist. Pharmacological Evidence for Cannabinoid Receptors in Glutamatergic Synapses at the Crayfish Neuromuscular Junction. *Pioneering Neuroscience*. 2005; 6:55–61.
15. International VP. Cesamet (nabilone) Capsule. 2006.
16. NDA. Marinol® (Dronabinol). 2004.
17. Physicians Total Care I. Marinol (dronabinol) capsule. Available from: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=fffb4e00-c921-4958-aeab-18deae4a2e38>
18. Munjal M, Elsohly MA, Repka MA. Polymeric systems for amorphous Delta9-tetrahydrocannabinol produced by a hot-melt method. Part II: Effect of oxidation mechanisms and chemical interactions on stability. *J Pharm Sci*. 2006 Nov; 95(11):2473–2485. PubMed PMID: 16886199. Pubmed Central PMCID: 2921982. Epub 2006/08/04. eng. [PubMed: 16886199]
19. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007 Aug; 4(8):1770–1804. PubMed PMID: 17712819. Pubmed Central PMCID: 2689518. Epub 2007/08/23. eng. [PubMed: 17712819]
20. Munjal M, Elsohly MA, Repka MA. Polymeric Systems for Amorphous (9)-Tetrahydrocannabinol Produced by a Hot-Melt Method. Part II: Effect of Oxidation Mechanisms and Chemical Interactions on Stability. *Journal of pharmaceutical sciences*. 2006; 95(11):2473–2785. PubMed PMID: PMC2921982. [PubMed: 16886199]
21. Hauss DJ. Oral lipid-based formulations. *Adv Drug Deliv Rev*. 2007 Jul 30; 59(7):667–676. PubMed PMID: 17618704. Epub 2007/07/10. eng. [PubMed: 17618704]
22. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. *Nat Rev Drug Discov*. 2007 Mar; 6(3):231–248. PubMed PMID: 17330072. Epub 2007/03/03. eng. [PubMed: 17330072]
23. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003; 42(4):327–360. PubMed PMID: 12648025. Epub 2003/03/22. eng. [PubMed: 12648025]
24. Huestis MA. Human Cannabinoid Pharmacokinetics. *Chemistry & biodiversity*. 2007; 4(8):1770–1804. PubMed PMID: PMC2689518. [PubMed: 17712819]

25. Thumma S, Majumdar S, Elsohly MA, Gul W, Repka MA. Preformulation studies of a prodrug of Delta9-tetrahydrocannabinol. *AAPS PharmSciTech*. 2008; 9(3):982–990. PubMed PMID: 18756377. Pubmed Central PMCID: 2977038. Epub 2008/08/30. eng. [PubMed: 18756377]
26. Souto EB, Mehnert W, Muller RH. Polymorphic behaviour of Compritol888 ATO as bulk lipid and as SLN and NLC. *Journal of microencapsulation*. 2006 Jun; 23(4):417–433. PubMed PMID: 16854817. [PubMed: 16854817]
27. Roberts M, Vellucci D, Mostafa S, Miolane C, Marchaud D. Development and evaluation of sustained-release Compritol(R) 888 ATO matrix mini-tablets. *Drug Dev Ind Pharm*. 2012 Sep; 38(9):1068–1076. PubMed PMID: 22149472. Epub 2011/12/14. eng. [PubMed: 22149472]
28. Patere SN, Desai NS, Jain AS, Kadam PP, Thatte UM, Gogtay N, et al. Compritol(R)888 ATO a lipid excipient for sustained release of highly water soluble active: formulation, scale-up and IVIVC study. *Curr Drug Deliv*. 2013 Oct; 10(5):548–556. PubMed PMID: 23607649. Epub 2013/04/24. eng. [PubMed: 23607649]
29. Sekulovic D. The effect of precirol ATO 5 on the properties of tablets. *Pharmazie*. 1987 Jan; 42(1): 61–62. PubMed PMID: 3575405. Epub 1987/01/01. eng. [PubMed: 3575405]
30. Saraiya D, Bolton S. The Use of Precirol® to Prepare Sustained Release Tablets of Theophylline and Quinidine Gluconate. *Drug Development and Industrial Pharmacy*. 1990; 16(13):1963–1969.
31. Hamdani J, Moës AJ, Amighi K. Physical and thermal characterisation of Precirol® and Compritol® as lipophilic glycerides used for the preparation of controlled-release matrix pellets. *International Journal of Pharmaceutics*. 2003 Jul 9; 260(1):47–57. [PubMed: 12818809]
32. Repka MA, Munjal M, ElSohly MA, Ross SA. Temperature Stability and Bioadhesive Properties of (9)-Tetrahydrocannabinol Incorporated Hydroxypropylcellulose Polymer Matrix Systems. *Drug development and industrial pharmacy*. 2006; 32(1):21–32. PubMed PMID: PMC2921171. [PubMed: 16455601]
33. FDA. Available from: http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_searchresults_dissolutions.cfm?printall=1
34. Thumma S, ElSohly MA, Zhang S-Q, Gul W, Repka MA. Influence of Plasticizers on the Stability and Release of a Prodrug of (9)-Tetrahydrocannabinol Incorporated in Poly (Ethylene Oxide) Matrices. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV*. 2008 Jun 18; 70(2):605–614. PubMed PMID: PMC2628598.
35. Witzleb R, Mullertz A, Kanikanti VR, Hamann HJ, Kleinebudde P. Dissolution of solid lipid extrudates in biorelevant media. *Int J Pharm*. 2011 Jan 17; 422(1–2):116–124. PubMed PMID: 22044538. Epub 2011/11/03. eng. [PubMed: 22044538]
36. Hofmann AF. Lipase, colipase, amphipathic dietary proteins, and bile acids: new interactions at an old interface. *Gastroenterology*. 1978 Sep; 75(3):530–532. PubMed PMID: 680521. Epub 1978/09/01. eng. [PubMed: 680521]
37. Blunk, T. Plasma protein adsorption. PhD Thesis. University of Kiel; 1994.
38. Blunk T, Hochstrasser DF, Sanchez JC, Muller BW, Muller RH. Colloidal carriers for intravenous drug targeting: plasma protein adsorption patterns on surface-modified latex particles evaluated by two-dimensional polyacrylamide gel electrophoresis. *Electrophoresis*. 1993 Dec; 14(12):1382–1387. PubMed PMID: 8137807. Epub 1993/12/01. eng. [PubMed: 8137807]
39. Brubach JB, Jannin V, Mahler B, Bourgaux C, Lessieur P, Roy P, et al. Structural and thermal characterization of glyceryl behenate by X-ray diffraction coupled to differential calorimetry and infrared spectroscopy. *Int J Pharm*. 2007 May 24; 336(2):248–256. PubMed PMID: 17207945. Epub 2007/01/09. eng. [PubMed: 17207945]
40. Armand M. Lipases and lipolysis in the human digestive tract: where do we stand? *Curr Opin Clin Nutr Metab Care*. 2007 Mar; 10(2):156–164. PubMed PMID: 17285003. Epub 2007/02/08. eng. [PubMed: 17285003]

Figure 1. Percentage THC released from the tablets as a function of type of the filler used in the composition. F-1 (DCPA); F-2 (Avicel); F-3 (Lactose). Each data point represents mean $\pm$ SD (n=3). Dissolution conditions: Basket apparatus operated at 100rpm, 37°C in 0.5% SLS medium.

Figure 2.

In vitro release profile of THC controlled release tablets (F-1) as a function of dissolution apparatus type and paddle/basket speed (rpm). Each data point represents mean $\pm$ SD (n=3). Dissolution conditions: Paddle, basket apparatus operated at 50rpm, 100rpm at 37°C in 0.5% SLS medium.

Figure 3.

In vitro release profile of THC as a function of lipid distribution between the matrix and/or blend phases of the formulation (basket, 100rpm). F-4: Precirol® distributed between matrix and blend; F-5: Precirol® in blend only. Each data point represents mean $\pm$ SD (n=3).

Dissolution conditions: Basket apparatus operated at 100rpm, 37°C in 0.5% SLS medium.

Figure 4.

In vitro release profile of THC from F-6 (Precirol® in the blend), F-7 (F-6 with Pluronic® F68), F-9 (Compritol® in the blend) and F-10 (F9 with Pluronic® F68) tablets. Each data point represents mean $\pm$ S.D. (n=3). Dissolution conditions: Basket apparatus operated at 100rpm, 37°C in 0.5% SLS medium.

Figure 5.

In vitro THC release from tablets prepared using a combination of lipids added to the blend phase. F-12 and F-14 contained Pluronic® F68. Each data point represents mean $\pm$ S.D. (n=3). Dissolution conditions: Basket apparatus operated at 100rpm, 37°C in 0.5% SLS medium.

Figure 6.

In vitro THC release profiles from 10 mg and 20 mg tablets. Each data point represents mean $\pm$ S.D. (n=6). Dissolution conditions: Paddle apparatus operated at 100rpm, 37°C in 0.5% SLS medium.

Table 1

Quantitative composition of the various formulations with the THC-lipid matrix *. Values represent mg/tablet.

Code	THC	Precirol® in Matrix	Compritol® in Matrix	Dibasic Calcium Phosphate Anhydrous	Avicel® in Blend	Ludipress® in Blend	Precirol® in Blend	Aerosil ® in Blend	Mg- Stearate in Blend
F-1	10	30		159.7				0.2	0.1
F-2	10	30			159.7			0.2	0.1
F-3	10	30				159.7		0.2	0.1
F-4	10	30		137.7			20	0.2	0.1
F-8	10		30	159.7				0.2	0.1

* All Formulations had the THC-lipid dispersion.

Table 2

Quantitative composition of the various formulations with no THC-lipid matrix *. Values represent mg/tablet.

Code	THC	Dibasic Calcium Phosphate Anhydrous	Pluronic® in Blend	Precirol® in Blend	Compritol® in Blend	Aerosil® in Blend	Mg. Stearate in Blend
F-5	10	159.7		30		0.2	0.1
F-6	10	129.7		60		0.2	0.1
F-7	10	127.7	2	60		0.2	0.1
F-9	10	129.7			60	0.2	0.1
F-10	10	127.7	2		60	0.2	0.1
F-11	10	149.7		30	10	0.2	0.1
F-12	10	147.7	2	30	10	0.2	0.1
F-13	10	149.7		20	20	0.2	0.1
F-14	10	147.7	2	20	20	0.2	0.1

* THC was coated on to the filler in all formulations and lipid added directly to blend with all other excipients.

Table 3

Tablet Hardness and THC Content Across Various Formulations. Hardness Values Represented in Kilopounds (kp) units.

Formulation #	Hardness	Content Uniformity		
		Mean (% content)	%RSD	Range
1	5.3 ± 0.8	102.3	5.4	Acceptable
2	5.2 ± 1.1	97.4	5.9	Acceptable
3	5.7 ± 0.3	100.7	5.7	Acceptable
4	5.3 ± 1.0	100.5	4.6	Acceptable
5	5.6 ± 1.4	100.6	3.4	Acceptable
6	5.3 ± 1.9	99.7	4.0	Acceptable
7	5.6 ± 0.4	96.6	4.1	Acceptable
8	5.3 ± 1.2	101.2	2.2	Acceptable
9	5.3 ± 0.7	97.9	5.6	Acceptable
10	5.4 ± 1.1	99.6	4.0	Acceptable
11	5.4 ± 0.8	98.3	4.1	Acceptable
12	5.7 ± 1.2	100.2	4.8	Acceptable
13	5.5 ± 0.6	101.8	4.5	Acceptable
14	5.4 ± 0.9	99.1	2.7	Acceptable

Table 4

FDA recommended dissolution conditions for the marketed THC formulations.

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)
Dronabinol	Capsule	II (Paddle)	100 and 150	10% Labrasol in Water; (In addition, the USP capsule rupture test should also be conducted)	500	5, 10, 15, 30, 45, 60, and until at least 80% of the labeled content is released
Nabilone	Capsule	II (Paddle)	50	0.1% Tween 80 solution	1000	15, 30, 45 and 60