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Full Length Research Paper

Some physical properties of novel *Cannabis* suppositories formulated with theobroma oil

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As part of development efforts for a suitable dosage form, crude *Cannabis* resin was formulated into suppository dosage form using theobroma oil and the physical properties of the suppositories were evaluated. The following physical properties were evaluated: appearance (texture, presence or absence of entrapped air, contraction holes), liquefaction time, uniformity of weight and *in-vitro* release profile of the crude marijuana resin from the suppositories. The torpedo shaped suppositories were smooth in texture with absence of entrapped air and contraction holes. The suppositories had uniform greenish brown colour and low weight variation. The liquefaction time was also low. The 300 mg *Cannabis* crude in 4 % Tween 85 showed highest melting time (11.67 ± 057 min) while the incorporation of Tween 85 improved the release profile (0.0452-0.0650 %) in different batches. It is possible to formulate marijuana suppositories with satisfactory physical properties; however, release profile of marijuana from the suppository bases was generally low even though the addition of Tween 85 greatly enhanced drug release.

Key words: Crude *Cannabis* resin, sustained release, liquefaction time, weight uniformity, release profile.

INTRODUCTION

There are anecdotal reports of *Cannabis* relieving the sign and symptoms of various disease conditions such as asthma, convulsion, multiple sclerosis (MS), ocular pressure, acute post-operative and intractable pain, as well as stimulating appetite and antispasmodic (Russo, 2011; Ben, 2006; Hazekamp and Grotenhermen, 2010; Noyes et al., 1975; Wade et al., 2003; Grant, 2001; Tomida et al., 2006; Formukong et al., 1988; Obonga, 2006; Regelson et al., 1976; Di Tomaso et al., 1996). Other medicinal values such as antiemetic and use in palliative or terminal care have been reported for inhaled *Cannabis* and oral tetrahydrocannabinol (THC) (Matsuda

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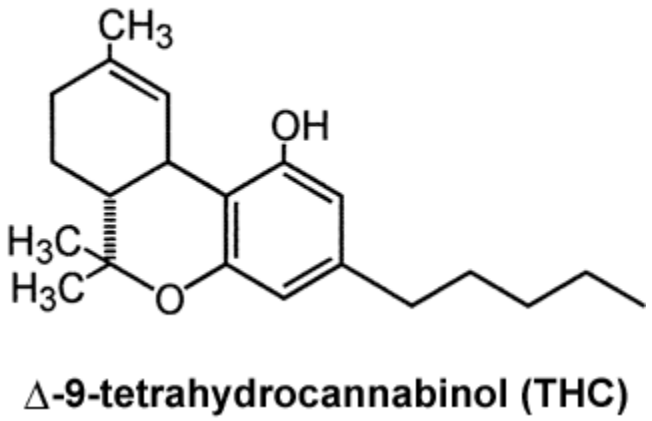

Figure 1. Chemical structure of marijuana

et al., 1990; Vincent et al.,1983; Salan et al., 1979; Vinciguerra et al., 1988; Consroe et al., 1996; Elsohly et al., 1985; Holister, 1971). Health hazards associated with *Cannabis*-based medicines are largely as a result of the difficulty that physicians encounter in obtaining consistent dose from batches of plant material of varying potency (Gierienger, 1999) and due to possible pathogens and microtoxins present in the *Cannabis* (Kagen et al., 1983; Taylor et al., 1982; Gordon et al., 2013). Consequently, patients suffer from ineffective (under) dose or the unwanted intoxication effects resulting from an over dose (British Medical Association, 1997). Modern techniques have attempted to solve this problem of quality control in the *Cannabis* phyto-medicines through plant breeding and cultivation. However, the issue of narrow therapeutic window between the desired benefits and the usual unwanted psychoactive effects remains a challenge (Institute of Medicine, 1999).

∆-9-Tetrahydrocannabinol, Δ^9-THC (Figure 1) (Grotenhermen, 2002), presently the most widely used and the major psychoactive constituent of *Cannabis*-based medicine, can be taken orally (Brennesisen, 2002) but absorption of THC from this oral route is very low and unreliable, especially when compared with the non-conventional method of smoking or inhaled by vaporization. Inhalation of *Cannabis* is a very efficient way of delivering the drug quickly and in manner that allows flexible dose titration (British Pharmacopia, 2001). Smoking, however, carries serious medical risks; the irritant effects of *Cannabis* smoke can lead to bronchitis and later to far more serious hazards such as lung cancer and many other bronchial diseases (Ashton, 2001).

In line with current trend in the scientific world, researches have shifted from isolation of pure active ingredients and structural determination and eventual synthesis of active compounds to formulation of the crude drugs. Experience has shown that pharmacological activity may not be resident in any of the components of the phyto-constituents but in the *Cannabis* resin as a whole. The current challenge in the medicinal application of *Cannabis* is therefore, the development of suitable dosage forms which would enhance the stability, convenience of administration and bioavailability of the drug.

Previous reports indicated efficient delivery of *Cannabis* and its derivatives to systemic circulation in formulations using different lipid carriers (Russo, 2002; Grant et al., 2012; Mattes et al., 1993). We realized that oral bioavailability of THC need not be low if there is a suitable lipid carrier, that smoking is not particularly efficient for its delivery from a pharmacokinetic standpoint, and that titration is hardly easy, particularly with modern Western strains of high potency, which tend to produce maximum psycho-activity with absorbed doses far in excess of those needed for medical symptom control. Hence the present study was aimed at evaluating some of the physical properties of theobroma oil-based suppositories containing crude *Cannabis* resin in a lipid carrier as part of formulation development process.

MATERIALS AND METHODS

Hydrochloric acid (BDH, England), theobroma oil (BP Pharmaceutical Grade), Tween® 85 (BDH, England) and crude *Cannabis* resin (extracted in our laboratory). Other reagents and solvents were of analytical grade and were used as such without purification.

Source and identity of plant materials

The fresh whole leaves of *Cannabis sativa* were collected and the plant was identified by a plant Taxonomist at the Crude Drug and Research Unit of the National Drug Law Enforcement Agency (NDLEA) Enugu, Enugu State of Nigeria.

Preparation of plant extracts

Whole leaves of *C. sativa* were rinsed thoroughly with purified water, shade-dried in open air for 48 h and pulverized to coarse powder. One thousand grams (1000 g) of the powdered leaves of *C. sativa* L. was extracted with 2.5 L of methanol (95% v/v) for 8 h using a soxhlet extractor (Gallenkamp, England). The crude methanolic extract was evaporated to dryness under reduced pressure, using a rotary evaporator (Gallenkamp, England) at an optimum temperature of between 40 and 45°C, to yield 173.25 g of crude resin tar.

Preparation of *Cannabis* formulations

Preparation of suppositories

Using the displacement value of 1.5 for theobroma oil, the correct quantity of the base for each batch was calculated. Six batches of the suppositories (three batches contained 300 mg of *Cannabis* crude resin with 2, 4 and 6% Tween® 85 and three batches of 300, 600 and 900 mg, respectively of crude *Cannabis* resin per suppository without Tween® 85 were prepared. Enough quantities to yield 12 suppositories per batch were calculated at each instant.

Table 1. Results of the physical parameters of the *Cannabis* crude resin extract suppositories

Batch	Parameters		
	Weight uniformity (g ± CV)	Liquefaction time (mean ± SD)	Absolute drug content (mg in Tween ® 85)
1	1.08 ± 2.91	11.00 ± 3.60	300 in 2% Tween® 85
2	1.04 ± 3.05	11.67 ± 0.57	300 in 4% Tween® 85
3	0.96 ± 6.54	10.00 ± 1.00	300 in 6% Tween® 85
4	1.04 ± 2.45	9.33 ± 0.57	300
5	1.04 ± 3.79	8.67 ± 0.57	600
6	1.09 ± 1.69	7.43 ± 1.25	900

CV = Coefficient of variation, SD = Standard deviation

The correct quantity of the drug was added to the base (after melting), with continuous stirring until it was cool but pourable. The preparation was poured into a 1.0 g mould (previously lubricated with glycerin) until there was an overflow and then cooled at 0°C for 30 min. After cooling, the suppositories were removed from the mould and stored in the refrigerator for further experiments.

Evaluation of suppositories

Appearance

Two suppositories were randomly selected from each batch and the external and internal surfaces when cut longitudinally examined with the naked eye and also with a hand lens. The suppositories were examined for the presence or absence of air bubbles, brittle fracture, uniformity of mixing and for presence or absence of contraction holes.

Uniformity of weight

Six suppositories were picked at random and weighed together using a torsion balance. They were also weighed individually and the mean, variance, standard derivation and coefficient of variation calculated.

Liquefaction time

Liquefaction time apparatus, which can also be used to determine the melting point of fatty base suppositories proposed by Setnikar and Fantelli (1962) was modified and used in this study. Each suppository was placed in a heat-resistance and inelastic polyethylene material and tied directly on the bulb of a thermometer using an in-extensible thread. The thermometer with suppository was inserted into a 0.1 N HCl solution maintained at 37 ± 0.1°C by means of a thermostatic heating mantle (Jurgen & Co.). The time taken for the suppository to melt at that temperature was recorded. Average of four determinations was taken as the liquefaction time.

Construction of calibration curve (Beer's plot)

Cannabis crude resin (100 mg) was weighed out and dissolved in 100 ml solution of ethanol to obtain a stock solution. From the stock solution, 0.1 ml was diluted to 100 ml with ethanol (concentration 0.1 mg %). Similarly, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0 to 2.0 ml of the stock were diluted to 100 ml to obtain the corresponding strengths in mg %. The absorbance of each diluted sample was determined at 274 nm using a UV/Vis spectrophotometer (UV 2102, Unico, USA). The absorbance values were plotted against the concentration to yield Beer's plot. The slope of the graph was determined. Validation of the method was performed to ensure that the calibration curve between 1 and 20 µg/ml was in the linearity range of the assay and the coefficients of variation were less than 2% both intra-day and inter-day.

Release studies

The Erweka dissolution test apparatus (Erweka, Germany) was used for the determination of the release rate of the suppositories. Each suppository was placed in the appropriate compartment of the dissolution apparatus containing 400 ml of 0.1 N HCl buffer solutions. The paddle was rotated at 120 rev/min and the dissolution medium was maintained at 37 ± 1°C. At predetermined time intervals, 5.0 ml samples were withdrawn and appropriately diluted. A 5.0 ml quantity of buffer solution (pre-warmed to the sink temperature of 37 ± 1°C) was added to the dissolution medium at each time interval to compensate for the sampling and maintain the sink conditions. The absorbances of the dilute solution were measured at 274 nm with a spectrophotometer, and the concentrations were determined from the calibration curve. Average of two-absorbance readings at each time interval was used for all batches.

RESULTS AND DISCUSSION

The suppositories were torpedo-shaped, smooth in texture with absence of entrapped air, contraction holes or brittle fracture. The external and internal surfaces of the suppositories were uniform in appearance when examined with the naked eye and hand lens. The uniformity in appearance was in terms of colour (greenish brown) and texture. This indicates satisfactory subdivision and dispersing of suspended material and all the batches passed the test according to British Pharmacopoeia (BP) specifications (British Pharmacopeia, 2001). The suppositories had uniform weights as shown in Table 1 (with the exception of batch 3). The coefficients of variations

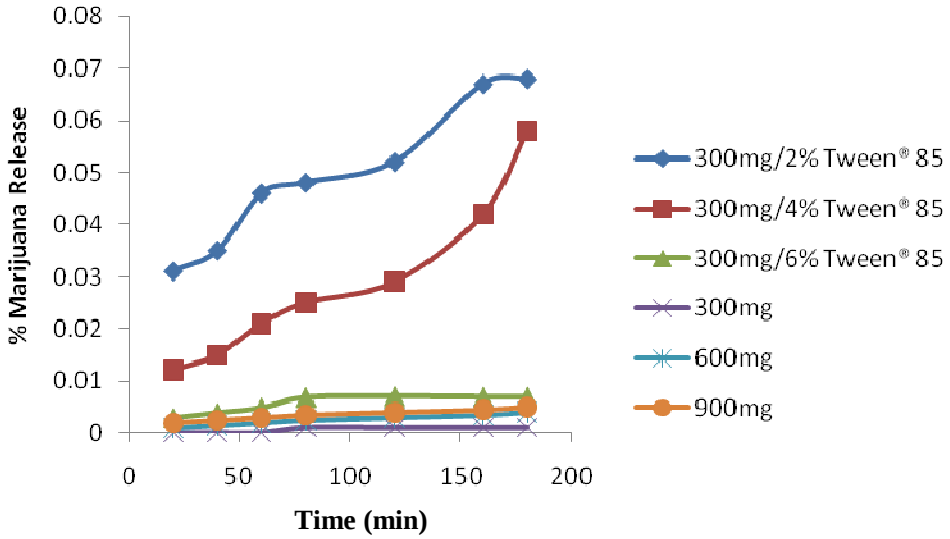

Figure 2. Release profile of crude *Cannabis* from the suppositories in 0.1 N HCl

of variation (CV) were low for all the batches. This indicates that the mixture of ingredients and the suppository base was fairly homogenous before pouring into moulds. Also, the variation in weight of the suppositories may have resulted from sedimentation of drug during pouring since the drug (that is *Cannabis*) was only dispersed in the base. All the batches (with the exception of batch 3) passed the test according to BP specifications (British Pharmacopeia, 2001). The liquefaction times were generally low. The knowledge of the liquefaction time is essential because a suppository which takes too long to liquefy may be expelled before liquefaction occurs together with the drug it contains. Besides, liquefaction time is analogous to disintegration time of tablets. A drug formulation that does not liquefy easily may be expelled before drug release occurs and may also exert a mechanical irritant action on the ampulla even if the base and the drug, per se are not irritant (Setnikar and Fantelli, 1962). The 300 mg *Cannabis* crude in 4% Tween 85 showed highest melting time (11.67 ± 057 min). This may be attributed to the heat resistance of Tween® 85, which modified the liquefaction of theobroma oil.

Figure 2 shows the release profile of *Cannabis* crude resin from the suppositories. The release of *Cannabis* crude was enhanced in batches 1 and 2 containing 2 and 6% of (0.065 and 0.0452% at 150 min) Tween® 85, respectively, while batches 4, 5 and 6% releases (0.0030, 0.0045 and 0.0057%, respectively at 150 min) were very low. This may be as the result of incorporation of various percentages of Tween® 85 into batches 1 to 3, while batches 4 to 6 had no Tween® 85 incorporated into them. It might be said that the release profile of *Cannabis* from the suppository bases was generally low even though the addition of Tween® 85 greatly increased drug release. While the results of this preliminary study appear promising, our team is currently on researches to ascertain the *in vivo* performances of the *Cannabis* suppositories in experimental animals and then humans to determine the levels of THC or cannabinoids in serum using modern analytical tools.

Conclusion

It is possible to formulate *Cannabis* suppositories with satisfactory physical properties using theobroma oil. The incorporation of polysorbate 85 increased *Cannabis* release from the suppository cavities by virtue of its ability to lower liquefaction time of the suppositories. However, the release rate was generally low from the suppositories, indicating sustained release potential.

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Conflict of interest

Authors report no conflict of interests.

REFERENCES

Ashton CH (2001). Pharmacology and effects of cannabis: a brief review. Br. J. Psychiatry 178(2):101–6.

Ben AM (2006). Cannabinoids in medicine: A review of their therapeutic potential. J. Ethnopharmacol. 105(1-2):1–25.

Brennesisen R (2002). Pharmacokinetics. In: Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential. The Haworth Integrative Healing Press®, an imprint of the Harworth Press, Inc. New York. pp. 67-72.

British Medical Association (1997). Therapeutic uses of Cannabis. Amsterdam: Harwood Academic Publishers.

British Pharmacopeia Commission (2001). British Pharmacopeia. Her Majesty's Stationary Office, London. P 457.

Consroe P, Musty R, Rein J, Tillery W, Pertwee R (1996). The perceived effects of smoked *Cannabis* on patients with multiple sclerosis. Eur. Neurol. 38:44-48.

Di Tomaso E, Beltramo M, Piomelli D (1996). Brain cannabinoids in chocolate. Nature 382(6593):677–8.

Elsohly MA, Harland E, Murphy JC, Wirth P, Waller CW (1985). Cannabinoids in glaucoma: a primary screening procedure. J. Clin. Pharmacol. 21:472S-478S.

Formukong EA, Evans AT, Evans FJ (1988). Analgesic and anti-inflammatory activity of constituents of *Cannabis sativa* L. Inflammation 12(4):361-371.

Gierienger D (1999). Medical *Cannabis* potency testing. Bull. Multidiscip. Assoc. Psychedelic Stud. 9(3):20-22.

Grant E (2001). Medical use of Cannabinoids for multiple sclerosis. Drug Inform. 22(4):25-28.

Gordon AJ, Conley JW, Gordon JM (2013). Medical consequences of marijuana use: a review of current literature. Curr. Psychiatry Rep. Rev. 15(12):419.

Grant I, Atkinson JH, Gouaux B, Wilsey B (2012). Medical marijuana: clearing away the smoke. Open Neurol. J. 6(1):18–25.

Grotenhermen F (2002). Effects of *Cannabis* and the Cannabinoids. In: *Cannabis* and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential. The Haworth Integrative Healing Press®, an imprint of the Harworth Press, Inc. New York. pp. 123-132.

Hazekamp A, Grotenhermen F (2010). Review on clinical studies with cannabis and cannabinoids 2005-2009. Cannabinoids 5(special):1–21.

Institute of Medicine (1999). Preface ix. In: Joy JE, Watson SJ, Benson JA (Eds.), Marijuana and medicine: Assessing the science base. Washington, DC: National Academic Press. pp. 176-189.

Kagen S, Kurup V, Sohnle P, Fink J (1983). Marijuana smoking and fungal sensitization. J. Allergy Clin. Immunol. 71(4):389–93.

Matsuda LA, Lolait SJ, Brownstein MJ (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 346:561-564.

Mattes RD, Shaw LM, Edling-Owens J, Engelman K, Elsohly MA (1993). Bypassing the first-pass effect for the therapeutic use of cannabinoids. Pharmacol. Biochem. Behav. 44(3):745–747.

Noyes R, Brunk SF, Avery DA, Canter AC (1975). The analgesic properties of A-9-tetrahydrocannabinol. Clin. Pharmacol. Ther.18:84-89.

Obonga WO (2006). Evaluation of Phyto-Chemical and Medicinal Properties of Cannabis sativa Linn. (Family: Moraceae). Ph.D Thesis, University of Nigeria, Nigeria.

Regelson W, Butler JR, Schulz J, Kirk T, Peek L, Green ML, Zalis MO (1976). Δ^9- THC as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In: Braude MC, Szara, S (Eds), The Pharmacology of Marihuana. Raven press, New York: Raven. pp. 763-776.

Russo E (2002). *Cannabis* treatments in obstetrics and gynecology: A historical review. J. Cannabis Ther. 2(3/4):5-35.

Russo EB (2011). Taming THC: potential *Cannabis* synergy and phytocannabinoid-terpenoid entourage effects. Br. J. Pharmacol. 163(7):1344–1364.

Setnikar I, Fantelli S (1962). Liquefaction time of rectal suppositories. J. Pharm. Sci. 51(6):566-571.

Taylor DN, Wachsmuth IK, Shangkuan Y, Schmidt EV, Barrett TJ, Schrader JS, Scherach CS, McGee HB, Feldman RA, Brenner DJ (1982). Salmonellosis Associated with *Marijuana*. N. Engl. J. Med. 306(21):1249–53.

Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, Robson PJ (2006). Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. J. Glaucoma 15(5):349-353.

Vincent BJ, McQuiston DJ, Einhorn LH (1983). Review of cannabinoids and their antiemetic effectiveness. Drugs 25 Suppl. 1:52-62.

Vinciguerra V, Moore T, Brennan E (1988). Inhalation marijuana as an antiemetic for cancer chemotherapy. N. Y. State J. Med. 88:525-527.

Wade DT, Robson P, House H (2003). A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin. Rehabil. 17:18–26.