

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization

International Bureau

(43) International Publication Date
08 April 2021 (08.04.2021)



(10) International Publication Number
WO 2021/067806 A1

(51) International Patent Classification:

A61K 9/00 (2006.01) A61K 9/70 (2006.01)

Published:

— with international search report (Art. 21(3))

(21) International Application Number:

PCT/US2020/054070

(22) International Filing Date:

02 October 2020 (02.10.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/910,255 03 October 2019 (03.10.2019) US

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: TRANSDERMAL DELIVERY OF DRONABINOL

(57) Abstract: Provided is a transdermal drug delivery system comprising dronabinol. The dronabinol transdermal delivery system provides a drug plasma concentration at predetermined rate for a predetermined period of time, offering a simplified therapeutic regimen by decreasing dosing frequency for the treatment and/or prevention of nausea and/or vomiting associated with, for example, chemotherapy.



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TRANSDERMAL DELIVERY OF DRONABINOL

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/910,255, filed October 3, 2019, which is incorporated by reference herein.

TECHNICAL FIELD

[0002] The present disclosure relates to treatment of nausea and vomiting, such as nausea and vomiting commonly experienced by patients undergoing chemotherapy.

BACKGROUND

[0003] Nausea and vomiting are the common side effects of cancer chemotherapy. Drugs such as dronabinol and 5-HT₃ receptor antagonists are recommended for the treatment of nausea and vomiting associated with cancer chemotherapy. At times, to prevent nausea and vomiting one or more drugs can be used (*See* Herrsted J., et al., 2016 Updated MASCC/ESMO Consensus Recommendations: Prevention of Nausea and Vomiting Following High Emetic Risk Chemotherapy. *Support Care Cancer*. 2017 Jan; 25(1):277-288. Epub 2016 Jul 22).

[0004] Dronabinol is a synthetic form of delta-9-tetrahydrocannabinol (delta-9-THC) in sesame oil. Dronabinol is approved for use in treating emesis, and is available as an oral capsule (MARINOL) and as an oral solution (SYNDROS). As stated in the package insert or drug label for the oral capsule of dronabinol the drug “is indicated for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. It is also indicated for the treatment of anorexia associated with weight loss in patients with AIDS” (*See* Label for NDA Marinol, Labeling, Label action date June 21, 2006 accessed on July 13, 2017, hereafter “Label”).

[0005] Many shortcomings are associated with the dronabinol oral capsule. The first challenge is the dosage regimen. For an antiemetic effect the following dosage regimen is recommended: 1 to 3 hours before the chemotherapy a first dose of 5mg/m² is administered orally. After chemotherapy drug is administered every 2 to 4 hours in total 4 to 6 doses per day. Depending on the clinical response, if the dose is not sufficiently effective then the dose is increased by increments of 2.5 mg/m² up to about 15 mg/m². This dosage regimen is inconvenient for patients who are already experiencing nausea and vomiting. A second challenge is that the pharmacologic response is dose related and there is interpatient variability. A third challenge is that at maximum dose the likelihood of disturbing psychiatric symptoms increases. A fourth challenge is that after oral administration dronabinol undergoes first pass hepatic metabolism and has high lipid solubility; therefore, of the administered

dose 10% - 20% reaches systemic circulation. Another challenge is that at room temperature the active ingredient dronabinol is unstable in the capsules, and so the capsules are packaged in a closed container and recommended storage is in refrigerator or between 8°C — 15°C (*See Label*). The dronabinol capsule is stable for only 3 months at room temperature. This is due to synthetic delta-9-THC exhibiting rapid oxidation and acid and basic degradation. Moreover, synthetic delta-9-THC also degrades more rapidly in light and at higher temperatures. Accordingly, if dronabinol capsules are not stored refrigerated and in the original container, the concentration of delta-9-THC in the capsules will decrease, potentially below the therapeutically required concentration.

[0006] Previous studies have been performed with naturally derived delta-9-THC from marijuana plant *cannabis Sativa L.* However, it is difficult to extract pure delta-9-THC from a plant source, such as *Sativa L.* This is caused by an adulteration of the extract by small amounts of another active cannabidiols (such as cannabinol, delta-8-THC, cannabidiol and cannabichromene) present in final product. Accordingly, the amount of THC in final extract is dependent on the extraction process which is important due to the psychoactive properties of THC, among other considerations. Alternatively, the synthetic form of delta-9-THC is developed under a more controlled procedure as opposed to the extraction process for its naturally derived counterpart. For example, synthetically produced delta-9-THC consists essentially of uncontaminated delta-9-THC that is not adulterated by the presence of other active cannabidiols. Therefore, the synthetic version of delta-9-THC is able to provide improved transdermal permeability as compared to previously published work with naturally derived delta-9-THC which demonstrates a maximum flux of 0.01 µg/cm²/hr through rat skin for naturally extracted delta-9-THC (U.S. Patent No. 6503532).

[0007] US Patent No. 6328992 is also related to the preparation of transdermal delivery of cannabinoids. However, this disclosure describes different cannabinoids in combination and does not describe the use of pure synthetic delta-9-THC alone. Furthermore, the '992 patent inventors describes the use of permeability enhancers which are not pharmaceutical grade and not included in U.S. Food and Drug Administration Inactive Ingredient Listing (FDA IIG). Therefore the disclosure of the '992 does not provide a composition with any pharmaceutical utility. Furthermore, the '992 patent describes the use of rat skin with 50% ethanol in receiving media for the transdermal permeability testing. However, ethanol destroys the dermis skin structure and can increase the in-vitro flux value thus providing results that are not germane to transdermal patches for pharmaceutical applications. For example, ethanol treated rat skin is almost ten time more permeable than human cadaver skin.

[0008] US Patent No. 8449908 provides delivery of the cumulative amount of 10000 ng THC in 96 hrs through the human cadaver skin. This amount represents the flux of 60 ng/cm²/hr. The patch area can be calculated using following equation:

$$\text{In-Vitro Flux (ng/cm}^2\text{/hr)} = (\text{Css (ng/mL)} * \text{CL (L/kg*hr)} * \text{BW(Kg)}) / \text{Patch Area (cm}^2\text{)}$$

$$\text{Patch Area (cm}^2\text{)} = (\text{Css (ng/mL)} * \text{CL (L/kg*hr)} * \text{BW (kg)}) / \text{In-Vitro Flux (ng/cm}^2\text{/hr)}$$

$$= (1.38 * 0.2 * 70 * 1000) / 60$$

$$= 322 \text{ cm}^2$$

[0009] In order to deliver a therapeutic dosage of 5 mg/day of delta-9-THC, a transdermal formulation would need to cover at least 325 cm² surface area of the patient's skin. This is an impractical patch size for any transdermal drug delivery system (TDDS).

[0010] Therefore, there is a need for an improved drug delivery system of dronabinol which can overcome above stated drawbacks associated with oral administration and naturally derived delta-9-THC. As provided herein, transdermal delivery of dronabinol comprising synthetic delta-9-THC can address the challenges associated with oral drug delivery.

BRIEF SUMMARY

[0011] The following aspects and embodiments thereof described and illustrated below are meant to be exemplary and illustrative, not limiting in scope.

[0012] In one aspect, a pharmaceutical composition comprising dronabinol in a dosage form for transdermal delivery is provided.

[0013] In an embodiment, the pharmaceutical composition comprises no additional antiemetic drug.

[0014] In an embodiment, dronabinol is in a form selected from the group consisting of co-crystals, amorphous, coated, crystalline, a salt, an isomer, a solid solution, a prodrug, an analog, a derivative, a metabolite, a solution, synthetic, an ethanol solution, and a naturally derived delta-9-tetrahydrocannabinol.

[0015] In an embodiment, dronabinol is in the composition at between about 0.01%-95% w/w or between about 0.01%-95% w/v.

[0016] In an embodiment, dronabinol is selected from a group consisting of amorphous dronabinol, crystalline dronabinol, co-crystals of dronabinol, coated dronabinol, and ethanolic solution of dronabinol in the range of 0.01%-95% w/w or w/v.

[0017] In an embodiment, dronabinol is in a salt form.

[0018] In an embodiment, the composition is formulated as transdermal liquid formulation, transdermal semisolid formulation and /or transdermal polymer matrix formulation.

[0019] In an embodiment, a carrier or an ingredient in effective amount either alone or in combinations thereof is included in the composition. In an embodiment, the carrier or ingredient is selected from the group consisting of solvents, gelling agents, polymers, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, and oxidants.

[0020] In an embodiment, the carrier or ingredient is in the composition in a range of between about 0.01% - 95% w/w or w/v.

[0021] In an embodiment, the pharmaceutical composition is formulated as a transdermal patch.

[0022] In an embodiment, the transdermal patch is selected from the group consisting of a reservoir patch, a micro-reservoir patch, a matrix patch, a pressure sensitive adhesive patch, and an extended release transdermal film.

[0023] In an embodiment, the pharmaceutical composition is formulated as microneedles.

[0024] In an embodiment, the microneedles are formulated as a transdermal patch.

[0025] In an embodiment, a method for the treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy comprises selecting a patient in need of treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy; and topically applying or instructing to topically apply the pharmaceutical composition as described herein, wherein the topically applying is performed at least once in a day.

[0026] In an embodiment, the composition is a liquid formulation and/or a semisolid formulation, wherein the topically applying is done two to six times in a day, once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week.

[0027] In an embodiment, the composition is topically applied once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, or once in ten days.

[0028] In an embodiment, topically applying provides a constant rate of delivery of the active components of the transdermal patch over a time period.

[0029] In an embodiment, topically applying provides a steady absorption rate of dronabinol over a time period.

[0030] In an embodiment, topically applying achieves a constant blood serum level of dronabinol over a time period.

[0031] In an embodiment, topically applying achieves a reduced variability in blood serum level of dronabinol over a time period relative to oral administration of a dronabinol over the time period.

[0032] In an embodiment, topically applying achieves a plasma concentration of dronabinol in a therapeutic range over a period of time.

[0033] In an embodiment, as method for the treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy and/or anorexia associated with weight loss in patients with AIDS comprises selecting a patient in need of the treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy and/or anorexia associated with weight loss in patients with AIDS; topically applying or instructing to topically apply the pharmaceutical composition described herein; wherein applying achieves topical delivery of dronabinol for the treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy and/or anorexia associated with weight loss in patients with AIDS.

[0034] In an embodiment, the pharmaceutical composition is topically applied once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, or once in ten days.

[0035] In an embodiment, the pharmaceutical composition is topically applied two to six times in a day, once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week.

[0036] In an embodiment, the pharmaceutical composition is a liquid formulation or a semisolid formulation.

[0037] In an embodiment, the pharmaceutical composition is a transdermal delivery system.

[0038] In addition to the exemplary aspects and embodiments described above, further aspects and embodiments will become apparent by reference to the drawings and by study of the following descriptions.

[0039] Additional embodiments of the present methods and compositions, and the like, will be apparent from the following description, drawings, examples, and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment of the present disclosure. Additional aspects and advantages of the present disclosure are set forth in the following description and claims, particularly when considered in conjunction with the accompanying examples and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] FIG. 1 is a graph showing the plasma concentration of a drug as a function of time, in hours, when delivered via the oral route (open circles) or the transdermal route (closed circles).

DETAILED DESCRIPTION

[0041] In transdermal drug delivery, a transdermal patch or transdermal composition is applied topically to the skin surface. Throughout the duration of topical application of a transdermal patch or transdermal composition drug is continuously released and delivered through the intact skin (via transcellular, intercellular and trans-appendageal routes) to achieve systemic effect. Therefore, once applied the transdermal composition or transdermal patch can deliver drug into systemic circulation throughout the day or even for more than one day depending on the duration of its application, which can be up to a week or longer.

[0042] Transdermal delivery can reduce the dosing frequency of dronabinol which is currently administered orally 4-6 times a day. Through transdermal delivery, transdermal compositions or transdermal formulations or transdermal patch of dronabinol can be applied topically to skin thereby delivering the drug throughout the duration of topical application. Depending on the requirement, duration of topical application and can be once in day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week. Therefore, transdermal delivery can overcome the multiple dose regimen of oral delivery by reducing the dosing frequency.

[0043] Moreover, in transdermal drug delivery drug is delivered slowly and continuously throughout the duration of topical application hence there are no peaks and troughs in drug plasma concentration which are associated with multiple dose administration in a day. Therefore, by transdermal delivery of dronabinol patients can have the therapeutic effect of the drug for extended period of time without drastic changes in drug plasma concentration.

[0044] In transdermal delivery drug is delivered into systemic circulation through the skin, it escapes the first pass hepatic metabolism therefore to achieve the desired therapeutic activity less drug is required, resulting into less adverse effects or side effects. Dronabinol has high lipid solubility and after oral administration undergoes hepatic first pass metabolism therefore of the administered dose 10% - 20% reaches systemic circulation hence, as compared to oral dose with transdermal delivery small dose of dronabinol can give the desired therapeutic effects and can also overcome the disturbing psychiatric symptoms associated with high dose.

[0045] Also, the transdermal delta-9-THC delivery described herein provides almost 10 times more in-vitro permeability through human cadaver skin using FDA IIG database for approved drug products listed ingredients, as compared to previous systems.

[0046] For example, according to FDA labels for Marinol (dronabinol capsule) were given to healthy volunteers (n=34; 20-25 years) twice a day under fasted condition, the following pharmacokinetic (PK) parameters were found (see Label).

Table 1. Summary of Marinol® PK parameters

BID Dose (mg)	Mean (S.D.) PK Parameters Value		
	C _{max} ng/mL	Median T _{max} (range) hr	AUC (0-12) ng*hr/mL
2.5	1.32 (0.62)	1.00 (0.50-4.00)	2.88 (1.57)
5	2.96 (1.81)	2.50 (0.50-4.00)	6.16 (1.85)
10	7.88 (4.54)	1.50 (0.50-3.50)	15.2 (5.52)

[0047] Additionally, according to the PK parameters, the maximum plasma concentration for oral delivery of 5 mg/day by dronabinol capsule is 1.32 ng/mL and for oral delivery of 20 mg/day the maximum plasma concentration is 7.88 ng/mL. The oral delivery PK values demonstrate a peak and valley in plasma concentration over time. In contrast to oral delivery, transdermal drug delivery delivers the drug molecule at predetermined rate and maintains constant average plasma concentration over time (FIG. 1).

[0048] The average plasma concentration is calculated in the following manner:

$$\text{Average Plasma Concentration for 5mg/day} = \text{AUC}_{(0-t)} / t = 2.88/12 = 0.24 \text{ ng/mL}$$

$$20\text{mg/day} = 15.2/12 = 1.27 \text{ ng/mL}$$

[0049] Therefore, transdermal drug delivery systems (TDDS) are calculated to deliver delta-9-THC, at average plasma concentrations of 0.24-1.27 ng/mL.

[0050] For the prevention of nausea and vomiting, the oral route is often not the most convenient. Patients are already experiencing nausea and vomiting and if they vomit shortly after the drug administration uncertainty remains whether the dose was absorbed or is vomited. On the other hand, transdermally dronabinol will be delivered through the skin which completely eliminates these kinds of uncertainties.

[0051] Moreover, there are various additional side effects, such as Central Nervous System (CNS) side effects, related to oral dronabinol capsule administration. The side effects are dose related and therefore patients receiving the oral dosage require close monitoring so that the dosage can be adjusted and reduced as needed.

[0052] Alternatively, the TDDS systems provided herein provide constant drug delivery at a predetermined and defined input rate. Therefore, the currently provided TDDS systems provide a constant average plasma concentration due to constant input rates and do not exhibit PK peaks and valleys in plasma concentration associated with orally delivered delta-9-THC. Accordingly, the currently provided TDDS systems are also not as likely to cause CNS side effects as compared to the

orally delivered counterparts. For example, adverse effects of delta-9-THC are not induced with a dosage of 7 mg/m² of delta-9-THC.

[0053] Furthermore, oral dosages must be provided 4 to 6 times per day instead of taking once a day in order to avoid adverse effects. Additionally, oral dosage undergoes first pass metabolism and only 10-20% of the oral dose becomes available in plasma, resulting an inefficient delivery method and a large loss of the active pharmaceutical. Moreover, in order to achieve therapeutic effect from any drug molecule, the drug should have continuous delivery to achieve steady state plasma concentration or a plasma concentration in therapeutic window (between minimum and maximum therapeutic effective concentration). Therefore, the TDDS systems for delta-9-THC provided herein address long felt and unmet needs in the field of cannabidiol based pharmaceuticals.

[0054] Also, transdermal delivery is easy, noninvasive and convenient. Administration of transdermal patch or transdermal composition does not require medical supervision as patients can topically apply the transdermal patch or transdermal composition themselves.

[0055] With respect to dronabinol it is expected that interpatient variability in pharmacologic response will be less with the transdermal delivery as drug plasma concentration can be controlled by controlling the rate of drug delivery from transdermal composition or transdermal patch. Alpha half-life of dronabinol is about 4 hours, by oral administration it gets rapidly metabolized in the body. In contrast, with transdermal delivery small amount of dronabinol can be delivered for longer duration than oral administration. Transdermal formulations of dronabinol also provide more abuse deterrence than immediate release dosage forms.

[0056] Moreover, in case of any adverse effect, side effect or emergency transdermal delivery gives the liberty to terminate the therapy anytime by taking off the transdermal patch or transdermal composition from skin.

[0057] As per above stated reasons for the prevention of nausea and vomiting associated with cancer chemotherapy transdermal delivery can provide patient friendly, simplified and convenient therapeutic regimen over traditional delivery systems. Transdermal delivery can reduce the dosing frequency of dronabinol. Depending on the necessity, dosing frequency can be once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week.

[0058] For the prevention of nausea and vomiting associated with cancer chemotherapy patients are prescribed with a variety of different drugs, some of which are administered multiple times a day. By formulating the antiemetic drug(s) in a transdermal patch or transdermal composition provides a much-simplified dosage regimen to patients who are already weak and tired due to chemotherapy. Depending on the necessity, dosing frequency of the transdermal patch or transdermal composition containing the drug can be once in a day, once in two days, once in three days, once in four days,

once in five days, once in six days, once in a week. It would be a great addition to the patient compliance.

[0059] Dronabinol is an unstable drug. Stability of dronabinol can be improved by preparation of dronabinol's co crystals, coating the dronabinol, dronabinol's crystals, amorphous form, and/or inert substances, and the like.

[0060] Transdermal drug delivery composition, that in one embodiment, are in the form of a transdermal patch or delivery system comprising dronabinol are contemplated... Transdermal delivery can provide drug plasma concentration at predetermined rate for a predetermined period of time with a simplified therapeutic regimen by decreasing dosing frequency. Preferably, without any limitation dronabinol is selected from group such as dronabinol's co crystals, dronabinol's amorphous form, coated dronabinol, dronabinol's crystalline form.

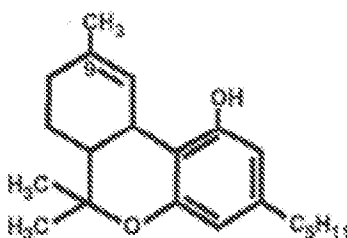
[0061] As used herein, "dronabinol" refers to all forms of dronabinol either alone or in combinations thereof, for example, in following forms but not limited to such as free base or salts or isomers or amorphous or crystalline or co-crystals or solid solution or prodrugs or analogs or derivatives or metabolites or coated form or natural extract of delta -9- tetrahydrocannabinol or synthetic delta-9-tetrahydrocannabinol, solution of dronabinol. For example, dronabinol's free form or its salts or its isomers or its amorphous form or its crystalline form or its co crystals or its solid solution or its prodrugs or its analogs or its derivatives or its metabolites or its coated form or natural extract of delta -9- tetrahydrocannabinol or synthetic delta-9-tetrahydrocannabinol, ethanolic solution of dronabinol. Dronabinol may be in the form of a pharmaceutically acceptable salt, such as an acid addition salt or a base salt, or a solvate thereof, including a hydrate thereof. Suitable acid addition salts are formed from acids which form non-toxic salts.

Chemical Name: (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-1-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

Empirical Formula: $C_{21}H_{30}O_2$

Molecular weight: 314.47

Structure: Formula 1



Formula 1

[0062] Dronabinol is synthetic delta-9-tetrahydrocannabinol. Delta-9-tetrahydrocannabinol is a natural component, present in Cannabis sativa L

[0063] In embodiments of the disclosure, without any limitation, a preferable form of dronabinol is selected from group such as dronabinol co-crystals, dronabinol amorphous form, coated dronabinol, dronabinol crystalline form. Dronabinol's co-crystals, coated dronabinol, dronabinol's crystalline form may be prepared.

[0064] Amorphous forms of the drug do not have a definite structure. An amorphous form of the drug has higher solubility as compared to a crystalline form. Different techniques and methods are used to make amorphous form of drugs.

[0065] As stated in regulatory classification of pharmaceutical co-crystals guidance for industry "Co-crystals are crystalline materials composed of two or more different molecules, typically drug and co-crystal formers ("coformers"), in the same crystal lattice" (See U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry Draft Guidance, Pharmaceutical Quality/CMC Revision 1, August 2016 <https://www.fda.gov/downloads/Drugs/Guidances/UCM516813.pdf>, accessed on July 12, 2017). Different methods are available for the preparation of co-crystals. Each drug has distinct chemical structure and physicochemical properties therefore, it is difficult to predict the success rate of co-crystallization reaction. Studies under various experimental conditions are done to determine an approach to form co-crystals of drug (See Nate Schultheiss, Ann Newman. Pharmaceutical Cocrystals and their Physicochemical Properties. Cryst Growth Des. 2009 Jun 3; 9(6): 2950-2967).

[0066] Coating of the drug can be done with polymer or other excipients. Different techniques are used for the coating of drug. Stability of the drug can also be increased by encapsulation.

[0067] As used herein, the term "pharmaceutically acceptable salts" includes acid addition salts or addition salts of free bases. The term "pharmaceutically acceptable salts" of the dronabinol within its scope all the possible isomers and their mixtures, and any pharmaceutically acceptable metabolite, bio-precursor and/or pro-drug, such as, for example, a compound which has a structural formula different from the one of the compounds of the disclosure, and yet is directly or indirectly converted in vivo into a compound of the disclosure, upon administration to a subject, such as a mammal, particularly a human being.

[0068] In one embodiment, dronabinol is incorporated into the transdermal system in the form of a pharmaceutically acceptable salt form, either as a single salt, as combinations of salts, or as a combination of the base form and one or more salt forms. Examples of the various forms of dronabinol include but not limited to such as free base, salts, racemic form, isomers, amorphous,

crystalline, co-crystals, solid solution, prodrugs, analogs, derivatives, metabolites, solutions, hydrates. Therapeutic agents may be in the form of a pharmaceutically acceptable salt, such as an acid addition salt or a base salt, or a solvate thereof, including a hydrate thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and without any limitation examples are acetate, hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, sodium phosphate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts. Suitable base salts are formed from bases which form non-toxic salts and without any limitation examples are the sodium, potassium, aluminum, calcium, magnesium, zinc and diethanolamine salts.

[0069] As used herein, the terms “subject” and “patient” are used interchangeably. As used herein, the term “patient” refers to an animal, preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey and human), and most preferably a human. In some embodiments, the subject is a non-human animal such as a farm animal (e.g., a horse, pig, or cow) or a pet (e.g., a dog or cat). In a specific embodiment, the subject is a human.

[0070] As used herein, the term “agent” refers to any molecule, compound, methodology and/or substance for use in the prevention, treatment, management and/or diagnosis of a disease or condition.

[0071] As used herein, the term “effective amount” refers to the amount of a therapy that is sufficient to result in the prevention of the development, recurrence, or onset of a disease or condition, and one or more symptoms thereof, to enhance or improve the prophylactic effect(s) of another therapy, reduce the severity, the duration of a disease or condition, ameliorate one or more symptoms of a disease or condition, prevent the advancement of a disease or condition, cause regression of a disease or condition, and/or enhance or improve the therapeutic effect(s) of another therapy.

[0072] As used herein, the phrase “pharmaceutically acceptable” means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia, or other generally recognized pharmacopeia for use in animals, and more particularly, in humans.

[0073] As used herein, the term “therapeutic agent” refers to any molecule, compound, and/or substance that is used for treating and/or managing a disease or disorder.

[0074] As used herein, the terms “therapies” and “therapy” can refer to any method(s), composition(s), and/or agent(s) that can be used in the prevention, treatment and/or management of a disease or condition, or one or more symptoms thereof. In certain embodiments, the terms “therapy” and “therapies” refer to small molecule therapy.

[0075] The term “derivative” or “derivatized” as used herein includes chemical modification of a compound of the disclosure, or pharmaceutically acceptable salts thereof or mixtures thereof. That is, a “derivative” may be a functional equivalent of a compound of the disclosure, which is capable of inducing the improved pharmacological functional activity in a given subject.

[0076] As used herein, the terms “composition” and “formulation” are used interchangeably.

[0077] As used herein, the term “topical delivery” means delivery of drug into systemic circulation through the skin.

Transdermal Compositions

[0078] According to certain embodiments, transdermal compositions described herein are for the prevention and/or treatment of nausea and/or vomiting associated with cancer chemotherapy.

[0079] According to certain embodiments described herein, the pharmaceutical composition or transdermal formulation contains dronabinol in a form selected from a group such as co-crystals, amorphous form, crystalline form, its coated form, its solution, and its salts which can be anhydrous and/or hydrous alone or in combinations thereof. More preferably the transdermal formulation may include dronabinol selected from following forms: amorphous or co-crystals or crystalline or coated or its ethanolic solution either alone or in combination of thereof.

[0080] One embodiment of the present disclosure can be a transdermal drug delivery system which may include without any limitation a transdermal formulation, a transdermal patch, a topical formulation, microneedles, iontophoresis, or a metered dose transdermal spray.

[0081] Transdermal formulation which includes liquids for example without any limitation like solutions, suspensions, dispersions, emulsion. Transdermal formulation includes semisolids for example without any limitations like gels, ointments, emulsions, creams, suspension, paste, lotion, balm. Liquid formulation and/or gel formulation incorporated in transdermal patch is preferred. Transdermal formulations which include a polymer matrix can be, without any limitation, an adhesive matrix or a non-adhesive matrix.

[0082] Without any limitation, transdermal patch may include all transdermal drug delivery systems stated in art preferably but not limited to reservoir patch, matrix patch, bilayer matrix patch, multilayer matrix patch, microreservoir patch, adhesive systems, transdermally applicable tape and other.

[0083] In certain embodiments of the present disclosure, a transdermal patch comprises dronabinol contained in a reservoir or a matrix, and an adhesive which allows the transdermal patch to adhere to

the skin, allowing the passage of the dronabinol from the transdermal patch through the skin of the patient. The transdermal delivery system can be occlusive, semi-occlusive or non-occlusive, and can be adhesive or non-adhesive.

[0084] In some embodiments, the transdermal patches provide for a constant rate of delivery of the active components of the transdermal patch over a predetermined time period. In some embodiments, the predetermined time period is about 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

[0085] In yet further embodiments, the transdermal patches described herein provide a steady absorption rate of the active components of the transdermal patches by the patient over a predetermined time. In some embodiments, the predetermined time period is 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

[0086] In yet further embodiments, the transdermal patches described herein provide a constant blood serum level of the active components of the transdermal patches in a patient over a predetermined time. In some embodiments, the predetermined time period is about 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

[0087] In yet further embodiments, the transdermal patches described herein provide a plasma concentration of the active components of the transdermal patches in a therapeutic range in a patient over a predetermined time. In some embodiments, the predetermined time period is about 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

[0088] In yet further embodiments, the transdermal patches described herein allow for reduced variability in dosage of active components in a patient over a predetermined time. In some embodiments, the predetermined time period is about 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 7 days, 8 to 13 days, two weeks, or 15 days.

[0089] The topical formulation stated in the art which include, for example without any limitation, semisolids such as ointment, cream, emulsion, micro emulsion, nano emulsion, paste, balms, gels, lotions, mousses. Liquids such as solutions, suspensions, micro suspension, nano suspension, dispersions, nano dispersion etc. Sprays, aerosols, magma, etc. The topical formulation comprising dronabinol can be topically applied to the skin surface for transdermal delivery of dronabinol.

[0090] The transdermal formulation and/or topical formulation of some embodiments of the present disclosure may include carriers or ingredients in effective amount either alone or in combinations

thereof without any limitation to the following carriers or ingredients such as solvents, gelling agents, polymers, biodegradable polymers, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, tackifiers, surfactants, volatile chemicals, antioxidants, oxidants, chelating agents, complexing agents, diluents, excipients, material to prepare patch, material to prepare a matrix patch or a reservoir patch.

[0091] Dronabinol may be dissolved, suspended, dispersed or uniformly mixed in the above stated single carrier, mixture of carriers and combinations of carrier.

[0092] The desired optimum transdermal and/or topical formulation of dronabinol may comprise without any limitation to following carriers as stated from Example 1 to Example 11 either alone or in combinations thereof.

EXAMPLES

Example 1

[0093] A transdermal formulation and/or topical formulation comprises solvents, alone or in combinations thereof, including but not limited to alcohol C1-C20 such as but not limited to (methanol, ethanol, isopropyl alcohol, butanol, propanol etc.), polyhydric alcohols, glycols such as but not limited to (propylene glycol, polyethylene glycol, dipropylene glycol, hexylene glycol, butylene glycol, glycerine etc.), derivative of glycols, pyrrolidone such as but not limited to (N methyl 2- pyrrolidone, 2-pyrrolidone etc.), sulfoxides such as but not limited to (dimethyl sulfoxide, decymethylsulfoxide etc), dimethylisorbide, mineral oils, vegetable oils, water, polar solvents, semi polar solvents, non-polar solvents, volatile chemicals which can be used to make matrix patch such as but not limited to (ethanol, propanol, ethyl acetate, acetone, methanol, dichloromethane, chloroform, toluene, IPA), acids such as but not limited to acetic acid, lactic acid, levulinic acid, fatty acids, bases and others. The mentioned solvents are, in an embodiment, in the range of 0.01% - 95% w/w or w/v.

Example 2

[0094] A transdermal formulation and/or topical formulation comprises gelling agents and/or thickening and/or suspending agents, alone or in combinations, including but not limited to natural polymers, polysaccharides and its derivatives such as but not limited to (agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium, or sodium carageenan, tragacanth, xanthan, gum copal, chitosan, resin etc.), semisynthetic polymers and its

derivatives such as without any limitation to cellulose and its derivatives (methylcellulose, ethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose etc.), synthetic polymers and its derivatives such as without any limitation to carboxyvinyl polymers or carbomers (carbopol 940, carbopol 934, carbopol 971p NF), polyethylene, and its copolymers etc, clays such as but not limited to (silicates, bentonite), silicon dioxide, polyvinyl alcohol, acrylic polymers (eudragit), acrylic acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyrrolidone copolymers such as but not limited to (PVP, Kollidon 30, Poloxamer), isobutylene, ethyl vinyl acetate copolymers, natural rubber, synthetic rubber, pressure sensitive adhesives such as silicone polymers such as but not limited to (bio-psa 4302, bio-psa 4202 etc.), acrylic pressure sensitive adhesives such as but not limited to (DURO-TAK 87-2156, DURO-TAK 387-2287, etc.), polyisobutylene such as but not limited to (polyisobutylene low molecular weight, polyisobutylene medium molecular weight, polyisobutylene 35000 mw, etc), acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers, etc. The mentioned agents are, in an embodiment, in the range of 0.1% 70% w/w or w/v.

Example 3

[0095] The transdermal formulation and/or topical formulation of the disclosure may comprise permeation enhancers known to those skilled in the art either alone or in combination thereof without any limitation to the following, such as sulfoxides, and similar chemicals such as but not limited to (dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide etc), azone, pyrrolidones such as but not limited to (N-methyl-2-pyrrolidone, 2-pyrrolidone etc.), esters, fatty acid esters such as but not limited to (propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, decyl oleate, glycerol monooleate, glycerol monolaurate, lauryl laurate etc.), fatty acids such as but not limited to (capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid etc.), alcohols, fatty alcohols and glycols such as but not limited to (oleyl alcohol, nathanol, dodecanol, propylene glycol, glycerol etc.), ethers alcohol such as but not limited to (diethylene glycol monoethyl ether), urea, triglycerides such as but not limited to triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers such as but not limited to (brij, sodium lauryl sulfate, tween, polysorbate), terpene, terpenoids and all penetration or permeation enhancers referred in the book "Percutaneous Penetration Enhancers" (*Eric W. Smith, Howard I. Maibach, 2005. Nov, CRC press*). The mentioned agents are, in an embodiment, in the range of 0.01% - 95% w/w or w/v.

Example 4

[0096] A transdermal formulation and/or topical formulation comprises plasticizers alone or in combination thereof, including without any limitation glycerol and its esters, phosphate esters, glycol derivatives, sugar alcohols, sebacic acid esters, citric acid esters, tartaric acid esters, adipate, phthalic acid esters, triacetin, oleic acid esters and all the plasticizers which can be used in transdermal drug delivery system referred in the book "Handbook of Plasticizers" (*George Wypych, 2004, Chem Tec Publishing*). The mentioned agents are, in an embodiment, in the range of 0.01% - 95% w/w or w/v.

Example 5

[0097] A transdermal formulation and/or topical formulation comprises emollients, humectants, and/or skin irritation reducing agents either alone or in combinations thereof without any limitation to following like petrolatum, lanolin, mineral oil, dimethicone, zinc oxide, glycerin, propylene glycol and others. The mentioned agents are, in an embodiment, in the range of 0.01% - 95% w/w or w/v.

Example 6

[0098] A transdermal formulation and/or topical formulation comprises solubilizers, surfactants, emulsifying agents, dispersing agents alone or in combination thereof without any limitation to following: surfactants, including anionic, cationic, nonionic and amphoteric surfactants, such as the sorbitan oleates under the trade name SPAN such as but not limited to SPAN 80, SPAN 20 etc. and the polysorbates such as but not limited to Polysorbate 20, Polysorbate 40, Polysorbate 60, Polysorbate 80 etc., propylene glycol monocaprylate type I, propylene glycol monocaprylate type II, propylene glycol dicaprylate, medium chain triglycerides, propylene glycol monolaurate type II, linoleoyl polyoxyl-6 glycerides, oleoyl-polyoxyl-6-glycerides, lauroyl polyoxyl-6-glycerides, polyglyceryl-3-dioleate, diethylene glycol monoethyl ether, propylene glycol monolaurate type I, polyglyceryl-3-dioleate, caprylocaproyl polyoxyl — 8 glycerides etc, cyclodextrins and others. The mentioned agents are, in an embodiment, in the range of 0.01% 95% w/w or w/v.

Example 7

[0099] Different techniques and ingredients can be used to increase the stability and/or solubility of dronabinol in the formulation such as without any limitation coating, encapsulation, microencapsulation, nanoencapsulation, lyophilization, chelating agents, complexing agents, etc.

Example 8

[0100] A transdermal formulation and/or topical formulation comprises auxiliary pH buffering agents and pH stabilizers and similar compounds known to those skilled in the art to maintain the appropriate pH of formulation preferably in the range of 4.0-8.0 either alone or in combination

thereof without any limitation to following such as phosphate buffer, acetate buffer, citrate buffer, etc., acids such as but not limited to (carboxylic acids, inorganic acids, sulfonic acids, vinyllogous carboxylic acids, fatty acids, and others), base such as but not limited to (sodium hydroxide, potassium hydroxide, ammonium hydroxide, triethylamine, sodium carbonate, sodium bicarbonate) etc. The mentioned agents are, in an embodiment, in the range of 0.01% - 30% w/w or w/v.

Example 9

[0101] A transdermal formulation and/or topical formulation comprises antioxidants, such as but not limited to, sodium metabisulfite, citric acid, ascorbic acid, BHA, and BHT, oxidizing agents, stabilizers, discoloring agents, preservatives and similar compounds or chemicals to provide a stable formulation. The mentioned agents are, in an embodiment, in the range of 0.01% - 50% w/w or w/v.

Example 10

[0102] A transdermal formulation and/or topical formulation with dronabinol formulated in ointment and/or cream base, gels, lotions, and other topical formulations.

Example 11

[0103] Materials to make the transdermal delivery system of the disclosure in patch form known to those skilled in the art, for example, such as but not limited to reservoir patch, matrix patch, drug in adhesives, transdermal films and may include, such as but are not limited to polymers, copolymers, derivatives, backing film, release membranes, release liners, etc. either alone or in combinations thereof. Pressure sensitive adhesives (such as but not limited to silicone polymers, rubber based adhesives, acrylic polymers, acrylic copolymers, polyisobutylene, acrylic acid – isoctyl acrylate copolymer, hot melt adhesives, polybutylene etc.), backing film (such as but not limited to ethylene vinyl acetate copolymers, vinyl acetate resins, polyurethane, polyvinyl chloride, metal foils, polyester, aluminized films, polyethylene, etc.), release membrane (such as but not limited to microporous polyethylene membrane, microporous polypropylene membrane, rate controlling ethylene vinyl acetate copolymer membrane etc.), release liners (such as but not limited to siliconized polyester films, fluoropolymer coated polyester film, polyester film, siliconized polyethylene terephthalate film, etc.), tapes, etc.

[0104] The transdermal formulation and/or topical formulation and/or transdermal delivery system of the disclosure may deliver at least therapeutic effective dose of dronabinol. Therapeutic effective dronabinol dose refers to the therapeutic concentration of dronabinol in human plasma required for treating and/or preventing nausea and/or vomiting associated with chemotherapy. Furthermore, the

precise therapeutic effective dose of dronabinol in the transdermal formulation or topical formulation or transdermal delivery system can be determined by those skilled in the art based on factors such as but not limited to the patient's condition etc. The transdermal formulation or topical formulation or transdermal delivery system will be available in different dosage strengths and patch sizes in order to achieve optimum therapeutic outcome based on patient's requirement.

[0105] In another embodiment, the transdermal formulation and/or topical formulation and/or transdermal delivery system of the disclosure may deliver at least therapeutic effective dose of dronabinol. Therapeutic effective dronabinol dose refers to the therapeutic concentration of dronabinol in human plasma required for treating as stated in MARINOL label "anorexia associated with weight loss in patients with AIDS" (*See Label*). Furthermore, the precise therapeutic effective dose of dronabinol in the transdermal formulation or topical formulation or transdermal delivery system can be determined by those skilled in the art based on factors such as but not limited to the patient's condition etc. The transdermal formulation or topical formulation or transdermal delivery system will be available in different dosage strengths and patch sizes in order to achieve optimum therapeutic outcome based on patient's requirement.

[0106] The transdermal formulation or transdermal patch of dronabinol preferably but not limited to can be applied to the skin surface in any of the following dosage regimens such as once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in a 8 to about 13 days, once in two weeks, once in 15 days.

Example 12

[0107] Synthetic delta-9-THC formulations for transdermal delivery (Formulation Nos. 001, 002, 006, 007, 008 and 009) were prepared by mixing ingredients as shown in Table 2:

Table 2: Transdermal Synthetic delta-9-THC formulations

Ingredients	001 (%W/V)	002 (%W/V)	006 (%W/V)	007 (%W/V)	008 (%W/V)	009 (%W/V)
TP	25					
PG	25	35	89.2	88.4	33	32.7
Water	20	20	9.9	9.9	33	32.7
Ethanol	29.5	44.5			33	32.7
THC	0.5	0.5	0.9	1.8	0.95	1.9

Abbreviations: TP = Transcutol P; PG = propylene glycol; THC = tetrahydrocannabinol.

[0108] All of the components from Table 2, with the exception of the THC, were mixed together with stirring for 18 hours. Next, the THC in ethanol was added into the excipient mixture to prepare the final transdermal formulations.

[0109] The prepared transdermal formulations were then subjected to a flux measurement test as follows. Human cadaver skin, stored at -80°C , was thawed at room temperature in phosphate buffered saline (PBS), and visually inspected for defects before using in the study. Transdermal flux was then measured using standard Franz diffusion cells composed of a cylindrical donor compartment and a separate water jacketed cylindrical receptor compartment with the volume of 13 mL. The human cadaver skin was clamped between the two compartments with the dermis side facing toward the receptor compartment. The donor compartment was filled with the transdermal THC formulations prepared as described above. The receptor compartment was filled with receptor medium, held at constant temperature, and constantly stirred to collect the THC as it diffuses through the skin and into receptor compartment. It is important to confirm that the receptor fluid is always in contact with the skin. The receptor compartment was emptied at 24 hr intervals for assay of delta-9-THC and replaced with fresh receptor solution. In order to maintain the sink condition in receptor compartment, it is important keep the delta-9-THC concentration in receptor compartment less than 10% of its solubility. The experimental conditions are provided in Table 3:

Table 3. Experimental Condition for In-vitro Permeability testing	
Receiving Media	De-ionized water + 0.5% Brij-O(20) +0.01% Sodium Azide
Receiving Media Volume (mL)	13
Sample Volume (mL)	13
Sampling Interval (hr)	24
Franz-cell diffusion area (sqcm)	1.76
Membrane Type	Human Cadaver Skin

[0110] Flux of THC through the human cadaver skin was measured for a minimum period of 96 Hrs (4 days) and results of the flux measurement are provided in Table 4.

Table 4. THC Flux Results

	001	002	006	007	008	009
Total Amount of THC Permeated at 96 hrs (ng/cm ²)	98700	154400	64200	122700	90900	102800
Flux (ng/cm ² /hr)	1000	1600	700	1300	950	1070
Patch Area (cm ²) (5 mg/day)	20	12	28	15	21	18

Example 13

[0111] Additional synthetic delta-9-THC formulations for transdermal delivery (Formulation Nos. 010 through 018) were prepared by mixing ingredients as shown in Table 5:

Table 5: Transdermal Synthetic delta-9-THC formulation nos. 010 to 018

Ingredients	010	011	012	013	014	015	016	017	018
	(%W/V)	(%W/V)	(%W/V)	(%W/V)	(%W/V)	(%W/V)	(%W/V)	(%W/V)	(%W/V)
THC	1.3	2.0	2.8	1.3	2.0	2.8	2.0	2.8	2.0
Ethanol	27.3	42.4	58.7	27.3	42.4	58.7	42.4	58.7	42.4
PG	64.3	50	34.6	71.4	55.6	38.5	-	-	-
Water	7.1	5.6	3.9	-	-	-	-	-	-
Dimethyl Sulfoxide (DMSO)	-	-	-	-	-	-	55.6	38.5	55.6

Abbreviations: THC = tetrahydrocannabinol; PG = propylene glycol.

[0112] Synthetic delta-9-THC formulations for transdermal delivery (010-018) were prepared by the same procedure described in Example 12. Flux measurement was also performed as described in Example 12. The experimental conditions are the same as provided in Table 3 of Example 12.

[0113] Flux of THC through the human cadaver skin was measured for a minimum period of 96 Hrs (4 days) and results of the flux measurement experiments are provided in Table 6.

Table 6. THC Flux Results

	Formulation No.								
	010	011	012	013	014	015	016	017	018
Total Amount of THC Permeated at 96 hrs (ng/cm ²)	75600 (31%)	94900 (20%)	102800 (52%)	54000 (33%)	145500 (63%)	204600 (43%)	35200 (22%)	35800 (1%)	53400 (6%)
Flux (ng/cm ² /hr)	800	1000	1070	600	1500	2100	400	400	600
Patch Area (cm ²) (5 mg/day)	24	19	18	32	13	9	48	48	32

Example 14

[0114] Additional synthetic delta-9-THC formulations for transdermal delivery (Formulation Nos. 019 to 027) were prepared by mixing ingredients as shown in Table 7.

Table 7: Transdermal Synthetic delta-9-THC formulation nos. 019-027

Ingredients	019 (% W/V)	020 (% W/V)	021 (% W/V)	022 (% W/V)	023 (% W/V)	024 (% W/V)	025 (% W/V)	026 (% W/V)	027 (% W/V)
THC	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Ethanol	42.4	42.4	42.4	42.4	42.4	42.4	42.4	42.4	42.4
PG	44.4	44.4	44.4	44.4	44.4	44.4	44.4	44.4	44.4
NMP	11.1								
Lauric acid		11.1							
Oleic Acid			11.1						
Lauryl Lactate				11.1					
Oleyl Alcohol					11.1				
GMO						11.1			
Lactic Acid							11.1		
HPC (Klucel®)								11.1	

Abbreviations: THC = tetrahydrocannabinol; PG = propylene glycol; NMP = n-methyl pyrrolidone; GMO = glycerol monooleate; HPC = hydroxypropyl cellulose.

[0115] Synthetic delta-9-THC formulations for transdermal delivery (019-027) were prepared by the same procedure described in Example 12. Flux measurement was also performed as described in Example 12. The experimental conditions are the same as provided in Table 3 of Example 12.

[0116] Flux of THC through the human cadaver skin was measured for a minimum period of 72 hours (3 days) and results of the flux measurement experiments are provided in Table 8.

Table 8. THC Flux Results

	Formulation No.								
	019	020	021	022	023	024	025	026	027
Total Amount of THC Permeated	56300 (10%)	29600 (82%)	20500 (14%)	5100 (29%)	5100 (22%)	26100 (34%)	36400 (92%)	31300 (19%)	31300 (16%)

at 72 hrs (ng/cm ²)									
Flux (ng/cm ² /hr)	800	400	300	70	70	400	500	400	400
Patch Area (cm ²) (5mg/day)	24	48	64	276	276	48	38	48	48

Example 15

[0117] Additional synthetic delta-9-THC formulations for transdermal delivery (Formulation Nos. 028 to 034) were prepared by mixing ingredients as shown in Table 9:

Table 9: Transdermal Synthetic delta-9-THC formulation nos. 028 to 034

Ingredients	028 (% W/V)	029 (% W/V)	030 (% W/V)	031 (% W/V)	032 (% W/V)	033 (% W/V)	034 (% W/V)
THC	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Ethanol	42.4	42.4	42.4	42.4	42.4	42.4	42.4
PG	27.8	27.8	27.8	27.8	27.8	27.8	27.8
1,3 Butanediol	27.8						
Dipropylene Glycol		27.8					
Hexylene Glycol			27.8				
PEG-400				27.8			
Tween-20					27.8		
Tween-80						27.8	
Span-20							27.8

[0118] Synthetic delta-9-THC formulations for transdermal delivery (formulation nos. 028 to 034) were prepared by the same procedure described in Example 12. Flux measurement was also performed as described in Example 12. The experimental conditions are the same as provided in Table 3 of Example 12.

[0119] Flux of THC through the human cadaver skin was measured for a minimum period of 120 hours (5 days) and results of the flux measurement experiments are provided in Table 10.

Table 10: Transdermal Synthetic delta-9-THC formulations

	Formulation Nos.						
	028	029	030	031	032	033	034
Total Amount of THC Permeated at 120 Hrs (ng/cm ²)	103400 (9%)	86400 (17%)	115300 (53%)	61400 (43%)	7400 (80%)	30100 (137%)	43800 (47%)
Flux (ng/cm ² /hr)	900	700	1000	500	60	300	400
Patch Area (cm ²) (5mg/day)	22	28	19	38	322	64	48

Example 16

[0120] Additional synthetic delta-9-THC formulations for transdermal delivery patches (Formulation Nos. 035 to 038) were prepared by mixing ingredients as shown in Table 11:

Table 11: Transdermal Synthetic delta-9-THC formulation nos. 035 to 038

Ingredients	035 (% W/W)	036 (% W/W)	037 (% W/W)	038 (% W/W)
THC	2.0	2.0	2.0	2.0
PG	27.8	27.8	27.8	27.8
Hexylene Glycol	27.8	27.8	27.8	27.8
Durotak 9301	42.4			
Durotak 2516		42.4		
Durotak 2207			42.4	
Silicone Adhesive				42.4

[0121] To prepare a transdermal patch containing synthetic delta-9-THC, all of the components from Table 11, with the exception of the THC, were mixed together with stirring for 18 hours. Next, the THC was added 30 minutes before spreading the formulation. The formulation was spread using a commercial benchtop spreader. Specifically, the formulation matrix is evenly spread onto an 8x14 inch sheet of release liner (such as 3M 9744) to a thickness of 0.5mm. The sheet is then placed in an oven at 100° F for one hour to evaporate off the ethyl acetate and ethanol adhesive solvent. An opaque backing membrane (such as 3M 9730 NR film) with low permeability to oxygen, for inhibition of photo and oxidative degradation, is then carefully applied to the sheet by hand to avoid formation of bubbles and voids. A circular die (1.5 inches diameter) was used to cut patches (7 cm²) for subsequent studies.

[0122] The general procedure for flux measurements of transdermal formulations in the examples above was as follows. The human cadaver skin, stored at -80 °C, was thawed at room temperature in PBS, and visually inspected for defects before use. Transdermal flux was measured using standard Franz diffusion cells composed of a cylindrical donor compartment and a separate water jacketed cylindrical receptor compartment with the volume of 13 mL. The human cadaver skin was clamped between the two compartments with the dermis side facing toward the receptor compartment. The general procedure for flux measurement of the transdermal adhesive patch is as follows. The release liner is peeled off the patch and the adhesive surface is applied to a piece of human cadaver skin (Example 16, Table 11 only). The transdermal patch was adhered to the skin with the patch on the side of the skin in contact with the donor compartment. The receptor compartment was filled with receptor medium, held at constant temperature, and constantly stirred to collect the THC as it diffuses from the adhered patch, through the skin and into receptor compartment. It was confirmed that the receptor fluid was always in contact with the skin. The receptor compartment was emptied at 24 hour intervals for assay of delta-9-THC and replaced with fresh receptor solution. In order to maintain the sink condition in receptor compartment, the delta-9-THC concentration in the receptor compartment was maintained at less than 10% of its solubility. The experimental conditions are the same as provided in Table 3 of Example 12.

CLAIMS

IT IS CLAIMED:

1. A pharmaceutical composition, comprising: dronabinol in a dosage form for transdermal delivery.
2. The pharmaceutical composition of claim 1, comprising no additional antiemetic drug.
3. The pharmaceutical composition of claim 1 or claim 2, wherein dronabinol is in a form selected from the group consisting of co-crystals, amorphous, coated, crystalline, a salt, an isomer, a solid solution, a prodrug, an analog, a derivative, a metabolite, a solution, synthetic, an ethanol solution, and a naturally derived delta-9-tetrahydrocannabinol.
4. The pharmaceutical composition of any one of claims 1 to 3 wherein dronabinol is in the composition at between about 0.01%-95% w/w or between about 0.01%-95% w/v.
5. The pharmaceutical composition of any one of claims 1 to 4, wherein dronabinol is selected from a group consisting of amorphous dronabinol, crystalline dronabinol, co-crystals of dronabinol, coated dronabinol, and ethanolic solution of dronabinol in the range of 0.01%-95% w/w or w/v.
6. The pharmaceutical composition of any one of claims 1 to 5, wherein dronabinol is in a salt form.
7. The pharmaceutical composition of any one of claims 1 to 6, formulated as transdermal liquid formulation, transdermal semisolid formulation and /or transdermal polymer matrix formulation.
8. The pharmaceutical composition of any one of claims 1 to 7, comprising a carrier or an ingredient in effective amount either alone or in combinations thereof selected from the group consisting of solvents, gelling agents, polymers, penetration enhancers, emollients, skin irritation reducing agents, buffering agents, pH stabilizers, solubilizers, suspending agents, dispersing agents, stabilizers, plasticizers, surfactants, antioxidants, and oxidants.
9. The pharmaceutical composition of claim 8, wherein the carrier or ingredient is in the composition in a range of between about 0.01% - 95% w/w or w/v.

10. The pharmaceutical composition of any one of claims 1-9, wherein the pharmaceutical composition is formulated as a transdermal patch.
11. The pharmaceutical composition of claim 10, wherein the transdermal patch is selected from the group consisting of a reservoir patch, a micro-reservoir patch, a matrix patch, a pressure sensitive adhesive patch, and an extended release transdermal film.
12. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is formulated as microneedles.
13. The pharmaceutical composition of claim 12, wherein the microneedles are formulated as a transdermal patch.
14. A method for the treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy, comprising:
 - selecting a patient in need of treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy; and
 - topically applying or instructing to topically apply the pharmaceutical composition of any one of claims 1-13,
 - wherein the topically applying is performed at least once in a day.
15. The method of claim 14, wherein the composition is a liquid formulation and/or a semisolid formulation, wherein the topically applying is done two to six times in a day, once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week.
16. The method of claim 14, wherein the composition is topically applied once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, or once in ten days.
17. The method of any one of claims 14-16, wherein said topically applying provides a constant rate of delivery of the active components of the transdermal patch over a time period.
18. The method of any one of claims 14-17, wherein said topically applying provides a steady absorption rate of dronabinol over a time period.
19. The method of any one of claims 14-17, wherein said topically applying achieves a constant blood serum level of dronabinol over a time period.

20. The method of any one of claims 14-19, wherein said topically applying achieves a reduced variability in blood serum level of dronabinol over a time period relative to oral administration of a dronabinol over the time period.
21. The method of any one of claims 14-20, wherein said topically applying achieves a plasma concentration of dronabinol in a therapeutic range over a period of time.
22. A method for the treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy and/or anorexia associated with weight loss in patients with AIDS, comprising:
 - selecting a patient in need of the treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy and/or anorexia associated with weight loss in patients with AIDS;
 - topically applying or instructing to topically apply the pharmaceutical composition of any one of claims 1-13,
 - wherein said applying achieves topical delivery of dronabinol for the treatment and/or prevention and/or control of nausea and/or vomiting associated with cancer chemotherapy and/or anorexia associated with weight loss in patients with AIDS.
23. The method of claim 22, wherein the pharmaceutical composition is topically applied once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, or once in ten days.
24. The method of claim 22, wherein the pharmaceutical composition is topically applied two to six times in a day, once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week.
25. The method of any one of claims 22-24, wherein the pharmaceutical composition is a liquid formulation or a semisolid formulation.
26. The method of any one of claims 22-24, wherein the pharmaceutical composition is a transdermal delivery system.

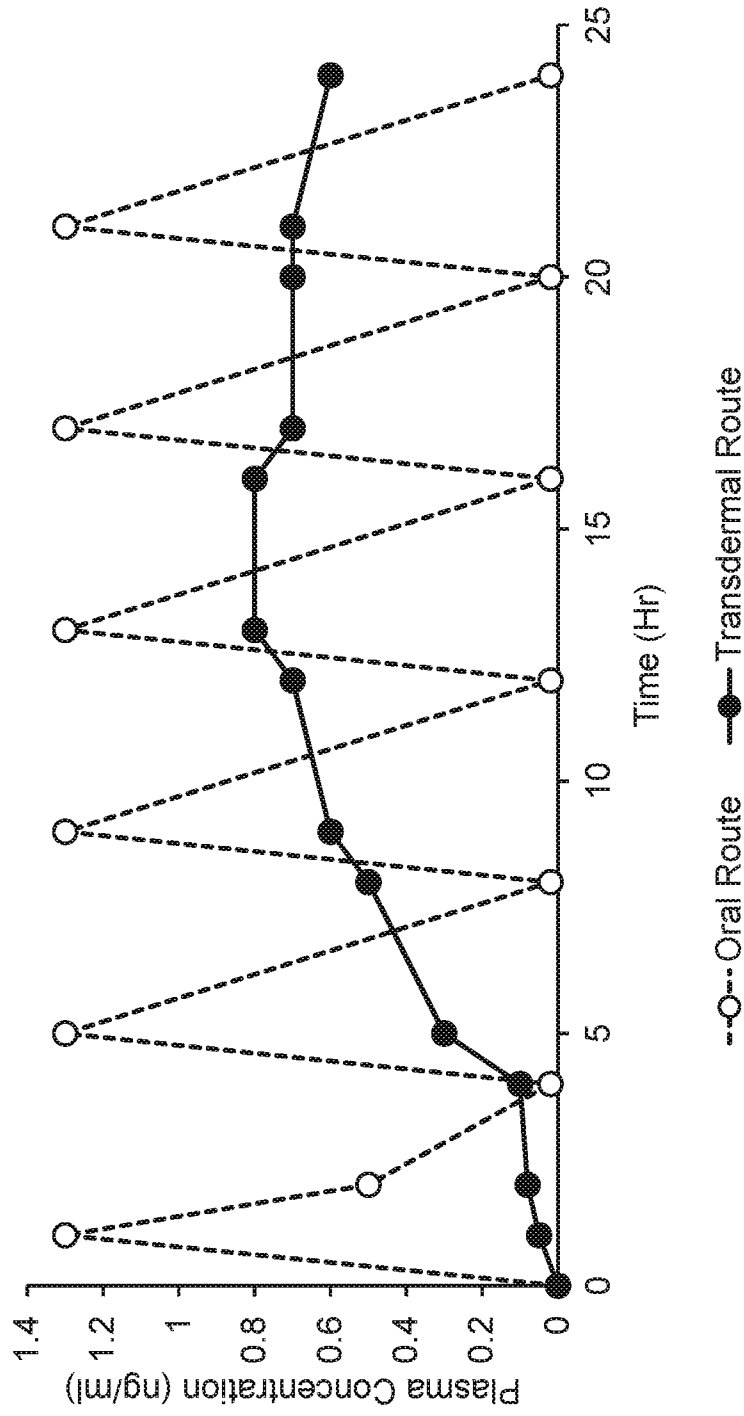


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/054070

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/70
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/124698 A2 (UNIMED PHARMACEUTICALS INC [US]; ROSE KEVIN [US]) 23 November 2006 (2006-11-23) claims 1-20	1-26
X	US 6 328 992 B1 (BROOKE LAWRENCE L [US] ET AL) 11 December 2001 (2001-12-11) claims 1-27	1-11, 13-26
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 24 December 2020	Date of mailing of the international search report 19/01/2021
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Schneider, Aurore
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/054070

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TOUITOU E ET AL: "Transdermal delivery of tetrahydrocannabinol", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER, NL, vol. 43, no. 1-2, 1 April 1988 (1988-04-01), pages 9-15, XP025544008, ISSN: 0378-5173, DOI: 10.1016/0378-5173(88)90052-X [retrieved on 1988-04-01] the whole document -----</p>	<p>1-11, 13-26</p>

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Information on patent family members

International application No

PCT/US2020/054070

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