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(54) **Title:** ORAL PHARMACEUTICAL FORMULATIONS OF ABUSE DETERRENT CANNABINOIDS AND METHOD OF USE

(57) **Abstract:** The present invention is directed to pharmaceutical compositions of cannabinoid agonists and the use thereof for preventing or minimizing the risk of cannabinoid agonist abuse and opioid agonist abuse. The present invention is also directed at a method of preventing or minimizing the risk of cannabinoid agonist abuse and opioid agonist abuse.

# ORAL PHARMACEUTICAL FORMULATIONS OF ABUSE DETERRENT CANNABINOIDS AND METHOD OF USE

## FIELD OF THE INVENTION

[0001] The present invention is in the field of oral compositions of cannabinoids and the use thereof.

## BACKGROUND OF THE INVENTION

[0002] Marijuana, often called "pot", "grass", "reefer", "weed", "herb", "mary jane" or "mj" is a greenish-gray mixture of the dried, shredded leaves, stems, seeds, and flowers of Cannabis sativa, the hemp plant. Most users smoke marijuana in hand-rolled cigarettes called "joints", among other names; some use pipes or water pipes called "bongs". Marijuana cigars called "blunts" have also become popular. To make "blunts", users slice open cigars and replace the tobacco with marijuana, often combined with another drug, such as "crack" cocaine. Marijuana also is used to brew tea and is sometimes mixed into foods.

[0003] The major active chemical in marijuana is delta-9-tetrahydrocannabinol (THC), which causes the mind-altering effects of marijuana intoxication. The amount of THC (which is also the psychoactive ingredient in hashish) determines the potency and, therefore, the effects of marijuana. Between 1980 and 1997, the THC content of marijuana available in the United States rose dramatically.

[0004] Marijuana is the most commonly used illicit drug in the United States. More than 94 million Americans (40 percent) age 12 and older have tried marijuana at least once, according to the 2003 National Survey on Drug Use and Health (NSDUH). Marijuana use is widespread among adolescents and young adults. It is reported that in 2004, 16 percent of 8th-graders volunteered that they had tried marijuana, and 6 percent were current users (defined as

having used the drug in the 30 days preceding the survey). Among 10th-graders, 35 percent had tried marijuana sometime in their lives, and 16 percent were current users. As would be expected, rates of use among 12th-graders were higher still. Forty-six percent had tried marijuana at some time, and 20 percent were current users.

[0005] The Drug Abuse Warning Network (DAWN), a system for monitoring the health impact of drugs, estimated that, in 2002, marijuana was a contributing factor in over 119,000 emergency department (ED) visits in the United States, with about 15 percent of the patients between the ages of 12 and 17, and almost two-thirds male.

[0006] In 2002, the National Institute of Justice's Arrestee Drug Abuse Monitoring (ADAM) Program, which collects data on the number of adult arrestees testing positive for various drugs, found that, on average, 41 percent of adult male arrestees and 27 percent of adult female arrestees tested positive for marijuana. On average, 57 percent of juvenile male and 32 percent of juvenile female arrestees tested positive for marijuana.

[0007] Cannabis use is world-wide public health issue. According to the United Nations Office for Drug Control and Crime Prevention (UNODCCP), Marijuana is the most widely used illicit drug in the world. It has been estimated that one in 11 cannabis users will become dependent (Anthony et al., Clin Psychopharmacol, 1994); rates of cannabis dependence in several countries (e.g., Australia, USA, South Africa) have increased substantially over the past decade (Bhana et al., S Afr Med J, 2002; SAMHSA, 2003), as well as the number of individuals seeking treatment (Stephens et al., Clin Psychol, 1993; Treatment Episode Data Set, 2002).

[0008] The principal psychoactive constituent of marijuana, THC, was not definitively identified until 1964 (Gaoni and Mechoulam, J Am Chem Soc, 1964). Unfortunately, marijuana is not a good source of THC due to the difficulties in isolation and purification. The development of a practical synthetic pathway (Razdan et al., Experientia, 1972) was a major boost to the subsequent pharmacological characterization of the effects of marijuana and

synthetic cannabinoids. Advances in chemistry, behavioral pharmacology, molecular pharmacology and neurobiology have facilitated the identification and characterization of an endogenous cannabinoid system.

[0009] Initial evidence of a cannabinoid receptor came from work that demonstrated enantioselectivity for a number of the effects of THC (Edery et al., Arzneim-Forsch, 1972; Little et al., Pharmacol Biochem Behav, 1989; Martin et al., Life Sci, 1981). More direct evidence for the receptor emerged from the work of Devane et al. (Mol Pharmacol, 1988) showing that a synthetic cannabinoid resulted in site specific avid binding in the brain. This and other discoveries raised the tantalizing possibility that an endogenous cannabinoid ligand may exist.

[0010] The work of Mechoulam resulted in the isolation of anandamide, a derivative of arachidonic acid. This endogenous ligand competed for cannabinoid receptor. Similar to THC, it inhibited electrically stimulated contractions in the murine vas deferens and produced pharmacological effects such as antinociception, catalepsy, hypomotility, hypothermia.

[0011] The endogenous cannabinoids or endocannabinoids are all eicosanoids. Examples include *N*–arachidonoylethanolamine (anandamide) and 2-arachidonoyl glycerol. Endocannabinoids, together with cannabinoid $CB_1$ and $CB_2$ receptors constitute the endocannabinoid system. The discovery of this endocannabinoid system has spurred research directed at elucidating the physiologic and pathophysiologic roles of the system and, importantly, at identifying targets for pharmacologic intervention in pathologic states.

[0012] It is now known that mammalian tissues express at least two cannabinoid receptors, both of which are G-protein coupled. These are $CB_1$ receptors and $CB_2$ receptors.

[0013] Although $CB_1$ receptors are expressed by some non-neuronal cells, including the pituitary, immune cells, and reproductive tissue, they are found primarily in peripheral and central nerve terminals where they mediate inhibition of neurotransmitter release. $CB_1$ receptors are expressed predominantly in the CNS with especially high levels in cerebellum,

hippocampus and basal ganglia. Indeed, of all neurotransmitters and hormone receptors, the $CB_1$ receptor is by far the most abundant. $CB_1$ receptors are also expressed to a much lesser extent in the peripheral nervous system as well as on the cells of the immune system, in the testis, heart and vascular tissues.

[0014] $CB_2$ receptors are found primarily on immune and hematopoietic cells outside (and also within) the central nervous system, where they appear to modulate cytokine release and immune cell migration.

[0015] Studies using $CB_1$ and $CB_2$ receptor knockout mice indicate that some of the effects of endocannabinoids are not mediated by either $CB_1$ or $CB_2$ receptors, suggesting the existence of additional yet to be identified sites of action. Some cannabinoid effects resist classification as either $CB_1$ and $CB_2$-mediated. Although some of these effects may not be mediated by specific receptors, there is growing evidence suggesting the involvement of additional receptors, which include $TRPV_1$ receptors and at least 2 G protein-coupled receptors (GPCRs) of unclear molecular identity that have only been defined pharmacologically (Wiley and Martin, Chemistry Physics of Lipids, 2002; Begg et al., Pharmacol Ther, 2005).

[0016] A number of pathologic states affect the human cannabinoid system, including Alzheimer's disease, schizophrenia, depression, alcoholism, Parkinson's disease, stroke, premature labor, endotoxic shock, hepatic cirrhosis, atherosclerosis, cancer, bone implantation, glaucoma, emesis, pain and pruritus of various etiology (Pertwee, AAPS Journal, 2005; Mackie Annu Rev Pharmacol Tox, 2006).

[0017] There are also signs of upregulation or downregulation of the endocannabinoid system in a variety of animal in vivo models, including multiple sclerosis, amyotrophic lateral sclerosis, encephalitis, Alzheimer's disease, Parkinson's disease, Huntington's disease, pain, obesity, feeding, fasting, stress, memory, aging, hypertension, cirrhosis, septic shock, cardiogenic shock, cerebral ischemia, myocardial infarction, neurotoxicity, febrile seizures and various intestinal disorders (Pertwee, AAPS Journal, 2005).

[0018] As a result of the large number of potential targets for pharmacologic intervention, efforts are underway to develop and test a variety of cannabinoid agonists and antagonists to prevent and treat various maladies. Presently, three non-specific cannabinoid receptor agonists are commercially available.

[0019] Nabilone (Cesamet™) and dronabinol (Marinol™) are oral synthetic THC analogs which have been shown effective for the treatment of nausea and vomiting associated with cancer chemotherapy and AIDS-related cachexia. They also possess analgesic, anti-hyperalgesic and anti-inflammatory properties mediated by the cannabinoid receptor(s), possibly by an uncharacterized $CB_2$-like cannabinoid receptor (Conti et al., Br J Pharmacol, 2002). Both drugs are scheduled under the Controlled Substances Act of 1970, as amended.

[0020] Unfortunately, nabilone and dronabinol produce a variety of effects including a number of psychotomimetic effects such as dizziness, drowsiness, euphoria, ataxia, anxiety, disorientation, depression, hallucinations, vertigo, and psychosis. While these psychic effects are undesirable for patients, they are often sought after by recreational drug users and individuals with an addiction disorder.

[0021] Addiction to drugs is characterized by long-lasting motivational disturbances including compulsive drug seeking, intense drug craving, use despite harm, the non-medical use and diversion of psychoactive substances, manipulation of the medical system and escalating drug use and risk taking behaviors. The neurobiological mechanisms underlying such behaviors are poorly understood. Cannabinoids play a modulatory role in drug seeking. An early signal came from the observation that the potent cannabinoid receptor agonist (6aR)-trans-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo [b,d] pyran-9-methanol was able to reinstate cocaine seeking behavior after several weeks of extinction of intravenous cocaine self-administration in the rat (De Vries, Nat Med, 2001). Further, this effect was completely abolished by the selective $CB_1$ receptor antagonist N-piperidinyl-

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl pyrazole-3-carboxamide, suggesting a role for cannabinoid agonists in cocaine relapse.

[0022] Similar effects have been shown in animals with a history of heroin, methamphetamine, alcohol and nicotine self-administration where cannabinoid receptor agonists have reinstated previously abolished drug seeking (De Vries et al, Psychopharmacology [Berl], 2003; Fattore et al, Eur J Neurosci, 2003; De Vries et al., Behav Brain Res, 2005; Anggadiredja et al., Neuropsychopharmacology, 2004).

[0023] Acute exposure of laboratory animals to cannabis extracts or cannabinoids produces a broad array of neurobiological effects including euphoria, sedation, analgesia, increased seizure threshold, memory impairment, hypothermia, appetite stimulation, motor inhibition, ataxia, incoordination, anxiety and antiemetic effects. Additionally, cannabinoids produce a number of peripheral effects, including hypotension, changes in adrenal function, immunosuppression, reductions in intraocular pressure and inflammation and gastrointestinal hypomotility (Chaperon et al., Critical Rev Neurobiol, 1999; Yamamoto et al., Jpn J Pharmacol, 2000; Maldonado et al, J Neurosci, 2002; Howlett et al., Neuropharmacol, 2004; Pertwee, AAPS Journal, 2005; Gonzalez et al., Pharmacol Biochem Behav, 2005; Mackie Annu Rev Pharmacol Tox, 2006)

[0024] There is reasonable consensus that following prolonged exposure to cannabinoids, pharmacologic tolerance laboratory animals. However, this development of tolerance has usually been observed when the cannabinoid is administered by the observer, rather in the setting of drug self-administration. In contrast to the laboratory setting, it is likely that such tolerance develops in the context of social cannabis use, with the possible exception of very heavy social use. It should be noted that another consequence of chronic cannabinoid exposure is the development of "behavioral sensitization", an attribute described previously in the literature for other drugs. This "behavioral sensitization" contributes to the increased drive and motivation for the drug substance that is being abused.

[0025] There exists considerable concern on the part of public health policy experts, addiction medicine specialists, pharmaceutical companies and government health regulators about the potential risk of drug abuse and drug diversion with the commercialization and widespread use of new cannabinoid agonists currently in development. Pharmaceutical companies have responded to the risk of abuse from cannabinoid agonists in different ways.

[0026] Some pharmaceutical companies with significant expertise in cannabinoid chemistry and discovery have elected to focus on therapeutic potential of cannabinoid antagonists to the exclusion of cannabinoid agonists.

[0027] Other pharmaceutical companies have decided to focus on $CB_2$ cannabinoid agonists since it is assumed that $CB_2$ receptors are found mainly outside of the brain, in immune cells and that $CB_1$ receptors are found throughout the body, but primarily in the brain.

[0028] However, the precise mechanism of action of $CB_2$ agonists is unknown and $CB_2$ agonists have also been found in the CNS. Additionally, there appear to be non-$CB_1$ and non-$CB_2$ mediated cannabinoid receptor agonism whose behavioral pharmacology has not been fully characterized (Howlett et al., Pharmacol Rev, 2002).

[0029] An important drawback with the use of cannabinoid agonist is the risk of drug addiction, drug diversion and drug abuse. For instance, unsuspecting clinicians may prescribe a cannabinoid agonist to patients who have an underlying, undisclosed addiction disorder. Alternatively, unsuspecting clinicians may prescribe a cannabinoid agonist to patients with a malady amenable to treatment or prevention with a cannabinoid agonist who in turn divert a portion of their prescribed dose to other individuals for non-medical use.

[0030] There have also been documented cases of inappropriate prescribing or dispensing of psychoactive drugs by physicians and pharmacists, with its eventual diversion into the non-medical marketplace. Additionally, experience with other classes of psychoactive, abusable drugs suggest that non-medical

supplies of pharmaceutical grade cannabinoid agonist will be available through prescription forgeries and break-ins into pharmacies.

[0031] Pharmaceutical dosage forms containing cannabinoid agonists will likely be used for non-medical purposes in a variety of settings: i) by patients with a malady amenable to treatment or prevention with a cannabinoid agonist who have developed an addiction disorder following initiation of the cannabinoid agonist; ii) by patients with an addiction disorder seeking cannabinoid agonists for their euphoriant properties and iii) by recreational drug users who may use cannabinoid agonists from time to time ("chippers") for pleasure seeking effects, analogous to the intermittent use of marijuana by many users.

[0032] Non-medical users of abusable drugs are either recreational drug users who may use such agents episodically, or individuals with an addiction disorder who may require frequent maintenance doses. Cannabinoid agonists may be ingested whole (intact) within the dosage limits, intact in excess of the dosage limits, crushed and ingested, crushed or vaporized and snorted, inhaled or injected intravenously after attempted extraction of the active, abusable pharmaceutical ingredient.

[0033] Addicts and recreational drug users commonly use abusable drugs by a variety of routes of administration. Common methods include 1) parenteral (e.g., intravenous injection), 2) intranasal (e.g., snorting), 3) inhalation, and 4) episodic or repeated oral ingestion of intact or crushed tablets or capsules.

[0034] One mode of abuse involves the extraction of the cannabinoid agonist component from the dosage form by first mixing the tablet or capsule with a suitable solvent (e.g., water or alcohol), and then filtering and/or extracting the cannabinoid agonist component from the mixture for intravenous injection. Another mode of abuse, especially for sustained or extended release cannabinoid agonist would involve dissolving the drug in water, alcohol or another "recreational solvent" to hasten its release, with the subsequent ingestion of the contents orally, in order to provide high peak concentrations and maximum euphoriant effects. Yet another mode of

abuse, for immediate and sustained release cannabinoid agonist would involve ingestion of the dosage form intact or after mechanical tampering at the usual medical doses or in excess of the medical doses. Yet another mode of abuse, for immediate and sustained release cannabinoid agonist would involve ingestion of the dosage form in any form and by any route in conjunction with other abusable drugs (e.g., opioid agonists)for additive effects. Yet another mode of abuse, for immediate and sustained release cannabinoid agonist would involve ingestion of the dosage form in any form and by any route in conjunction with other abusable drugs (e.g., opioid agonists) for synergistic effects.

[0035] A number of strategies have been introduced to minimize the abuse of mood altering drugs. Primary among these schemes is a legal infrastructure that controls the manufacture, distribution and sale of such drugs. In the United States, the vast majority of drugs, including cannabinoid agonists that have clinically useful and approved uses are restricted to dispensing on a prescription-only basis. Most of these drugs are "scheduled" as "controlled drugs", such that distribution of the drug is subject to strict controls and overview. The idea behind scheduling drugs as "controlled" is to ensure that the drugs are dispensed only for the amelioration of legitimate therapeutic maladies, and not for any mood-altering effect "high" or euphoria that may be produced by the drug when used in supra-therapeutic doses or administered by non-approved routes or methods of administration.

[0036] While the scheduling of cannabinoid agonists will reduce diversion and abuse of drugs, it is unlikely to be entirely successful. For example, some persons who are legitimately prescribed the drugs sometimes divert the drugs to persons seeking their procurement for "recreational uses." These "recreational drug users" are frequently willing to pay significant sums of money for the drugs. In other cases, certain health professionals, unfortunately, have been found to be culprits in the non-approved distribution of controlled drugs. In yet other cases, the illicit source of controlled drugs is through

unauthorized importation and smuggling from countries with less controlled distribution channels and through pharmacy break-ins.

[0037] It is believed that the most widely used diversion techniques at the "street level" are "doctor shopping" and prescription forgeries. In the case of the former, individuals who may or may not have a legitimate ailment requiring a doctor's prescription for controlled substances visit numerous doctors, sometimes in several states, to acquire large amounts of controlled substances they abuse or sell to others.

[0038] Scheduling of cannabinoid agonist also has the unintentional consequence of causing physicians, fearful of being accused of permitting "overuse", to prescribe suboptimal doses of the drugs to patients in need of them, and to prescribe less effective drugs to patients that are not similarly scheduled. This fear of prescribing for legitimate medical conditions amenable to treatment with pharmaceutical cannabinoid agonist is likely to grow as new cannabinoid therapeutics become commercially available. We have coined this phenomenon as "cannabinophobia" or "cannabiphobia".

[0039] There is a growing recognition in the medical community that a large number of patients suffer from the undertreatment of their medical condition when the treatment involves the use of psychoactive drugs, particularly those drugs which tend to diverted and abused. Pain is one example of such a medical condition amenable to treatment with abusable psychoactive agents such as cannabinoid agonists. Among the reasons frequently cited for undertreatment of pain, for example are: (1) the failure to prescribe enough drug at the right dosage interval to reach a steady-state threshold commensurate with the pain relief needed; and (2) the reluctance of many physicians to prescribe analgesics categorized as controlled substances based on concerns about addiction and fear of regulatory sanctions. For example, it has been reported that with respect to cancer pain, a large percentage of cancer patients suffer debilitating pain despite treatment with analgesics (Cleeland et al., New England Journal of Medicine 1994;330:592-596).

[0040] Cannabinoids hold substantial promise for the prevention and treatment of a wide variety of medical conditions, including multiple sclerosis, amyotrophic lateral sclerosis, encephalitis, Alzheimer's disease, Parkinson's disease, Huntington's disease, pain, obesity, feeding, fasting, stress, schizophrenia, depression, alcoholism, stroke, premature labor, endotoxic shock, hepatic cirrhosis, atherosclerosis, pruritus of various etiology and cancer.

[0041] Therefore cannabinoid agonists are going to be widely used for a variety of pathologic states.

[0042] Cannabinoid agonists also have the potential to create a major epidemic of drug abuse involving an entirely new pharmacologic class of agents.

[0043] The abuse of pharmaceutical dosage forms of cannabinoid agonists will in many cases involve: (i) use of the cannabinoid agonist dosage form in intact or tampered form as the sole abuse drug (e.g., extraction of the cannabinoid with the use of mechanical [e.g., crushing, shearing, grinding, chewing], thermal [e.g., heating, melting], or chemical [e.g., organic and aqueous solvent extraction] energy, followed by administration orally, intranasally, inhalationally, parenterally or sublingually]; and (ii) use in conjunction with opioid agonists.

[0044] There are no described abuse or misuse deterrence methods for cannabinoid agonists, including coadministration with opioid antagonists.

[0045] Recently, a buccal spray containing THC and cannabidiol (Sativex™) was approved in Canada for the symptomatic relief of neuropathic pain in multiple sclerosis (April, 2005) and for the treatment of cancer pain unresponsive to opioids (August, 2007). The prescribing information warns physicians that the drug *"should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence. Multiple substance abuse is common and marijuana, which contains the same active compounds, is a frequently abused substance. Therefore, SATIVEX® is not recommended in patients with addiction and drug abuse liability."* The

prescribing information states about the following effects: *"Following mild THC intoxication, symptoms include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following moderate THC intoxication, symptoms include memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following severe THC intoxication, symptoms include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders."*

[0046] There are no described abuse or misuse deterrence methods for cannabinoid agonists.

[0047] There is a need for novel methods of deterring or preventing cannabinoid agonist abuse.

[0048] There is a need for novel methods of deterring or preventing cannabinoid agonist abuse using multimodal abuse deterrent strategies.

[0049] There is therefore a need for abuse deterrent, and generally safer dosage forms of cannabinoid agonists which deter abuse by antagonizing concurrently or contemporaneously used or abused substances that are not part of the dosage form, such as opioid agonists.

## DETAILED DESCRIPTION OF THE INVENTION

[0050] It is an object of some embodiments of the invention to provide an oral dosage form of a cannabinoid agonist that is useful for decreasing the potential abuse of the cannabinoid agonist without affecting the therapeutic effects of the cannabinoid agonist.

[0051] It is an object of some embodiments of the invention to provide an oral dosage form of a cannabinoid agonist that is useful for decreasing the potential abuse of the cannabinoid agonist without affecting the therapeutic effects of the cannabinoid agonist or incurring the risk of precipitating signs and symptoms of cannabinoid withdrawal.

[0052] It is an object of some embodiments of the invention to provide an oral dosage form of a cannabinoid agonist that is useful for decreasing the potential abuse or co-abuse of concurrently used opioid agonist without affecting the therapeutic effects of the cannabinoid agonist or incurring the risk of precipitating signs and symptoms of cannabinoid withdrawal.

[0053] It is an object of some embodiments of the invention to provide an oral dosage form containing an effective dose of a cannabinoid agonist along with a dose of an opioid antagonist which does not significantly change the therapeutic efficacy of the cannabinoid agonist, but which has a significantly reduced potential for abuse and diversion.

[0054] It is an object of some embodiments of the invention to provide an oral dosage form containing an effective dose of a cannabinoid agonist which has a significantly reduced potential for abuse of the cannabinoid agonist or any concurrently or contemporaneously consumed, abused or co-abused opioid agonists.

[0055] It is an object of some embodiments of the invention to provide an oral dosage form containing an effective dose of a cannabinoid agonist and the use thereof for preventing or minimizing the risk of cannabinoid agonist toxicity from excessive use, abuse and overdose in cannabinoid agonist users and abusers who use or abuse opioid agonists.

[0056] It is an object of some embodiments of the invention to provide an oral dosage form containing an effective dose of a cannabinoid agonist and the use thereof for preventing or minimizing the risk of cannabinoid agonist abuse and/or opioid agonist use, abuse or co-abuse by drug addicts, recreational drug users, and opioid tolerant (e.g., opioid habituated) individuals.

[0057] It is an object of some embodiments of the invention to provide an oral dosage form containing an effective dose of a cannabinoid agonist and the use thereof for preventing or minimizing the risk of cannabinoid agonist abuse and/or opioid agonist use, abuse or co-abuse by drug addicts and/or recreational drug users.

[0058] Cannabinoid agonists of the present invention can be formulated to provide their medically intended therapeutic effects, while deterring their abuse, misuse and diversion and their co-abuse with opioids by co-administering them with opioid antagonists.

[0059] It is an object of some embodiments of the invention to provide an oral dosage form containing an effective dose of a releasable cannabinoid agonist and a substantially releasable opioid antagonist.

[0060] In some preferred embodiments, the dosage form is not directed at deterring or reducing the abuse potential of the cannabinoid agonist contained therein by direct pharmacologic antagonism of cannabinoid action by the opioid antagonist; instead, the opioid antagonist of the dosage form is intended to indirectly deter abuse, misuse, diversion and tampering of the cannabinoid agonist by antagonizing the effects of co-abused opioid agonists which are not part of the dosage form of the invention but which are present in systemic circulation as co-abused drugs in the setting of polydrug abuse.

[0061] In other embodiments, the dosage form is directed at deterring or reducing the abuse potential of the cannabinoid agonist contained therein by direct pharmacologic antagonism of cannabinoid action by the opioid antagonist.

[0062] In yet other embodiments, the dosage form is directed at deterring or reducing the abuse potential of the cannabinoid agonist contained therein by direct pharmacologic antagonism of cannabinoid action by the opioid antagonist and also intended to indirectly deter abuse, misuse, diversion and tampering of the cannabinoid agonist by antagonizing the effects of co-abused opioid agonists which are not part of the dosage form of the invention but which are present in systemic circulation as co-abused drugs in the setting of polydrug abuse.

[0063] It is an object of some embodiments of the invention to provide an oral dosage form containing an effective dose of a releasable cannabinoid agonist and a substantially releasable opioid antagonist, said dosage form effective in discouraging or preventing the unapproved or surreptitious use of

pharmaceutical grade or "street" grade opioid agonists for their mood altering effects by individuals who are recreational drug users, drug addicts, poly-drug abusers and individuals who have been expressly informed by their clinicians not to take opioid analgesics due to a risk of misuse or addiction or due a contraindication to opioid agonists.

[0064] It is an object of some embodiments of the invention to partially or substantially nullify the mood altering, rewarding and pleasurable psychic effects of opioid agonists in individuals who are prescribed cannabinoid agonists of the present invention and who are using said opioid agonists without the approval or medical supervision of their physician. The object of the invention is achieved by combining a releasable cannabinoid agonist and a substantially releasable opioid antagonist into an oral dosage form.

[0065] It is an object of some embodiments of the invention to reduce the potential for misuse and abuse of the oral cannabinoid agonist dosage form, when the dosage form is used in conjunction with the misuse or abuse of medically unauthorized or illicit opioid agonists. This is objective is achieved by exploiting the phenomenon of cannabinoid use and abuse in the setting of polydrug abuse, often involving opioid agonist abuse, said opioid agonists obtained via legitimate prescriptions, diversion from medical sources and illicit, non-medical sources. In the setting of polydrug abuse, the oral dosage form of the invention provides a substantial disincentive to use the cannabinoid agonist dosage form in conjunction with the misuse or abuse of medically unauthorized or illicit opioid agonists. In the setting of polydrug abuse, the oral dosage form of the invention provides are reduction in the overall pharmacologic benefit of cannabinoid abuse. In the setting of polydrug abuse, the oral dosage form of the invention extracts an economic penalty from the recreational drug user and drug abuser by diminishing the "desirable" psychic effects of the opioid agonist paid for by the user. In the setting of polydrug abuse, the oral dosage form of the invention reduces the drug liking score and the street value of the dosage form.

[0066] It is an object of some embodiments of the invention to reduce the potential for misuse and abuse of the oral cannabinoid agonist dosage form when taken orally at medically recommended doses and in untampered form in the setting of polydrug abuse involving opioids.

[0067] It is an object of other embodiments of the invention to reduce the potential for misuse and abuse of the oral cannabinoid agonist dosage form when taken orally at in excess of medically recommended doses and untampered form (e.g. by a non-oral route) in the setting of polydrug abuse involving opioids.

[0068] It is an object of yet other embodiments of the invention to reduce the potential for misuse and abuse of the oral cannabinoid agonist dosage form only when taken by the non-oral route (e.g., parenteral, intranasal, inhalational).

[0069] In some embodiments, the greater the amount of the dosage form abused with opioid agonists, the greater the nullification of opioid agonist effects.

[0070] In some embodiments, abuse of the dosage form, especially in large quantities, produces signs and symptoms of opioid withdrawal.

[0071] In particularly preferred embodiments, the dosage form contains opioid antagonists with low or intermediate oral bioavailability, thereby having a particularly pronounced opioid blocking or opioid nullification effect when given by routes of administration that partially bypass first pass gastrointestinal and hepatic metabolism (e.g., intravenous, inhalational and intranasal administration).

[0072] In some embodiments, abuse deterrence is obtained not by any direct action of the opioid antagonist on the cannabinoid agonist; instead, the inclusion of an opioid antagonist in the oral dosage form containing the cannabinoid agonist is a strategic intervention to exploit the patterns of drug abuse and co-abuse by nullifying or minimizing the effects of opioid agonist present in the systemic circulation of the polydrug abuser. Additionally, the

oral dosage form of the invention also reduces the toxicity observed in the setting of intentional abuse, accidental abuse and overdose.

[0073] In some embodiments of the invention, the substantially releasable opioid antagonist of the dosage form has low or negligible bioavailability by the oral route. However when taken in excess by the oral route or when taken at usual or excessive doses by a non-oral route following manipulation or tampering of the dosage form (e.g., physical, chemical, thermal manipulation or solvent extraction, followed by intravenous, inhalational or intranasal administration), the opioid antagonist of the dosage form reduces or nullifies the mood altering effects of the cannabinoid agonist of the dosage form, even when the cannabinoid agonist is the sole abused drug.

[0074] The efficacy of the abuse deterrence is greater when the amount of the oral dosage form of the invention which is co-abused is increased. The efficacy of the abuse deterrence is also greater when the dosage form is abused by parenteral, intranasal or inhalational routes, as is frequently the case in drug hard core and habitual drug addicts. The efficacy of the abuse deterrence is also greater when the dosage form is abused by opioid tolerant individuals, individuals who abuse large doses of opioids and individuals with habitual or intractable abuse, opioid abuse and polydrug abuse

[0075] In some preferred embodiment, the present invention exerts abuse deterrence properties of a pharmacologic nature only in the presence of an opioid agonist in the human body. However, in view of: (i) the significant co-use and co-abuse of opioid agonists with cannabinoid agonists; and (ii) the opportunistic nature of drug abuse (i.e., abuse of drugs which are available in the illicit market place at the desired time and price, which we have coined: "drug of abuse *du jour*", 'drug *du jour*", and "abuse *du jour*"), there is frequent use or impending use of cannabinoid agonists with opioid agonists. Consequently, even in the absence of an opioid agonist in the systemic circulation, the possibility of the impending presence of the opioid agonist provides a powerful psychological abuse deterrence. In other embodiments, the present invention exerts abuse deterrence properties of a pharmacologic

nature versus the cannabinoid agonist. In yet other embodiments, the present invention exerts abuse deterrence properties even in the absence of opioid agonists by reducing the craving and desire for opioid agonists.

[0076] In some embodiments, the present invention is directed at oral dosage forms of a cannabinoid agonist and the use thereof for preventing or minimizing the risk of polydrug toxicity from use of the dosage form by the oral route at the usual medically recommended dose, in conjunction with the misuse or abuse of medically unauthorized or illicit opioid agonists, and from tampering of the dosage form, wherein the cannabinoid agonist of the dosage form is co-abused with one or more opioid agonist toxicity in the setting of polydrug abuse.

[0077] In some embodiments, the present invention is directed at oral dosage forms of a cannabinoid agonist and the use thereof for indirectly deterring cannabinoid agonist abuse by drug addicts and/or recreational drug users by providing an aversive effect solely to the co-abused opioid agonist in the setting of polydrug abuse.

[0078] In some embodiments, the present invention is directed at oral dosage forms of a cannabinoid agonist and the use thereof for deterring opioid agonist diversion into the illicit drug market for use, abuse and misuse by drug addicts and/or recreational drug users in the setting of polydrug abuse.

[0079] It is an object of some embodiments of the invention to provide an oral dosage form of a cannabinoid agonist that is useful for decreasing the potential abuse of the cannabinoid agonist without significantly affecting the therapeutic effects of the cannabinoid agonist or incurring the risk of precipitating signs and symptoms of cannabinoid agonist withdrawal.

[0080] It is an object of some embodiments of the invention to provide an oral dosage form of a cannabinoid agonist along with a dose of opioid antagonist which does not worsen the safety of the cannabinoid agonist, but which when used in conjunction with the medically unauthorized or illicit opioid agonists, can prevent abuse by interfering with the effect of the co-abused opioid agonist.

[0081] It is an object of some embodiments of the invention to provide an oral dosage form of a substantially releasable cannabinoid agonist with a dose of a substantially releasable opioid antagonist that nullifies the effect of any co-administered or co-abused opioid agonist, thereby: (i) deterring the misuse, diversion and abuse of the dosage form; (ii) deterring the abuse of the cannabinoid agonist in the dosage form; (iii) deterring abuse of any co-abused opioid agonist; (iv) deterring polydrug abuse; (vi minimizing or eliminating the polydrug toxicity upon ingestion of the dosage form after tampering; and (v) minimizing or eliminating the mood altering additive "benefits" of the cannabinoid agonist in drug addicts and recreational drug users upon ingestion of the dosage form after: (a) use of the dosage form as directed but in conjunction with the use, misuse or abuse of medically unauthorized or illicit opioid agonists; and (b) tampering of the dosage form (e.g, extraction of the cannabinoid agonist followed by non-oral administration).

[0082] It is an object of some embodiments of the invention to provide a method for preventing abuse of an oral dosage form containing a releasable cannabinoid agonist and a substantially releasable opioid antagonist both when the dosage form is administered intact but in conjunction with the misuse or abuse of medically unauthorized or illicit opioid agonists, and after tampering of the dosage form containing the cannabinoid agonist and opioid antagonist (e.g., in an attempt to misuse the dose of cannabinoid agonist after solvent extraction, intravenous administration, intranasal and inhalational administration).

[0083] It is an object of some embodiments of the invention to provide a method for preventing abuse of an oral dosage form containing a releasable cannabinoid agonist and a substantially releasable opioid antagonist, e.g., when the dosage form is administered intact, it nullifies the effect of any co-administered or co-abused opioid agonists, and further nullifies the effects of any co-administered or co-abused opioid agonist when the dosage form is tampered with (e.g., in an attempt to extract the cannabinoid agonist from the

dosage form for oral, inhalational, intravenous or intranasal misuse), thereby reducing the motivation to abuse the dosage form.

[0084] It reasons that the nullification of the pharmacologic effects of the opioid agonist will be more robust (e.g., faster onset, higher peak, longer duration, greater intensity) when the contents of the dosage form are tampered with (e.g., in an attempt to extract the cannabinoid agonist from the dosage form for oral, inhalational, intravenous or intranasal misuse) and then ingested, compared with the use of the intact dosage form by an opioid abuser.

[0085] It is an object of some embodiments of the invention to provide an oral dosage form containing a releasable cannabinoid agonist and a substantially releasable opioid antagonist intended for or suitable for use in the management of acute or chronic diseases or disorders where alteration of the cannabinoid agonist's therapeutic effects must be avoided, as in cases of tolerance, physical dependence or individual variability in hepatic metabolism or physiology.

[0086] It is an object of some embodiments of the invention to provide a method of treating diseases or disorders in human subjects with an oral dosage form of a cannabinoid agonist, while reducing its misuse and the incentive for misuse by oral, parenteral, intranasal, inhalational and/or sublingual route.

[0087] In some embodiments, the present invention involves an oral dosage form comprising a mixture of a cannabinoid agonist and an opioid antagonist, the opioid antagonist being present in an amount sufficient to substantially reduce or eliminate (or nullify) the pharmacological effect of opioid agonists co-abused by cannabinoid abusers in the setting of polydrug abuse. In some embodiments, the present invention provides abuse deterrence even when there is no co-abused opioid agonist in systemic circulation of the abuser a the time of the abuse of the dosage form by reducing or negating the mood altering benefits of the cannabinoid agonist therein or in other embodiments, any future opioid agonist which might be abused within minutes, hours or days of ingestion of the intact or tampered dosage form of the invention, i.e., while the opioid antagonist is still present in systemic circulation.

[0088] Some or all of the above objects and others are achieved by embodiments of the present invention, which is directed in part to an oral dosage form comprising a cannabinoid agonist and an opioid antagonist, wherein the opioid antagonist is present in a partially or substantially releasable form or in a fully releasable form.

[0089] It is an object of some embodiments of the invention to provide a method for preventing misuse and abuse of an oral cannabinoid agonist dosage form where the dosage form also includes a dose of an opioid antagonist which is not sequestered, e.g., is substantially releasable in the gastrointestinal tract in conditions of ordinary use.

[0090] It is an object of some embodiments of the invention to provide a method for preventing misuse and abuse of opioid analgesics which are frequently co-abused with cannabinoid agonists by formulating an oral cannabinoid agonist dosage form where the dosage form also includes a dose of an opioid antagonist which is not sequestered, e.g., is substantially releasable in the gastrointestinal tract under conditions of ordinary use.

[0091] In some preferred embodiments, the oral dosage form contains: (i) an orally therapeutically effective amount of the cannabinoid agonist, the dosage form providing a desired therapeutic effect and (ii) an opioid antagonist which is present in a substantially releasable form (e.g., is co-released with the cannabinoid agonist into the gastrointestinal tract following disintegration and diffusion or dissolution or diffusion of the oral dosage form).

[0092] In some embodiments, the oral dosage form of the present invention is directed to an oral dosage form comprising (i) a cannabinoid agonist in releasable form and (ii) an opioid antagonist which is in a substantially releasable form, wherein the oral bioavailability of the opioid antagonist is less than about 1%, or less than about 2%, or less than about 3%, or less than about 5%, or less than about 8%, or less than about 10%, or less than about 15%, or less than about 20%, or less than about 25%, or less than about 30%, or less than about 35%, or less than about 40%, or less than about 50%, or less than about 60%, or less than about 70%, or less than about 80%, or less

than about 90%, or less than about 95%, or less than about 98%, or less than about 100%.

[0093] In some preferred embodiments, the oral dosage form contains: (i) an orally therapeutically effective amount of the cannabinoid agonist, the dosage form providing a desired therapeutic effect and (ii) an opioid antagonist which is present in a substantially releasable form (e.g., is co-released with the cannabinoid agonist into the gastrointestinal tract following disintegration and diffusion or dissolution of the oral dosage form), wherein the opioid antagonist has low or moderate oral bioavailability (e.g., an oral bioavailability relative to the intravenous route of less than about 1%, or less than about 1%, or less than about 3%, or less than about 5%, or less than about 8%, or less than about 10%, or less than about 15%, or less than about 20%, or less than about 25%, or less than about 30%, or less than about 35%, or less than about 40%, or less than about 50%, or less than about 60%, or less than about 70%. Preferably, said oral bioavailability is less than about 50% or less than about 40%, or less than about 30%, or less than about 20% or less than about 10%.

[0094] In some preferred embodiments, the oral dosage form contains: (i) an orally therapeutically effective amount of the cannabinoid agonist, the dosage form providing a desired therapeutic effect and (ii) an opioid antagonist which is present in a substantially releasable form (e.g., is co-released with the cannabinoid agonist into the gastrointestinal tract following disintegration (as applicable) and dissolution or diffusion of the oral dosage form), wherein the opioid antagonist is not significantly absorbed into the systemic circulation (e.g, due to low oral bioavailability, low absolute bioavailability, high intrinsic clearance, high first-pass metabolism, etc). Preferably, the opioid antagonist in the oral dosage form is substantially absorbed or found in systemic circulation when (abused or) administered by non-oral routes of administration which partially or substantially bypass first pass hepatic metabolism (e.g., intravenously, intranasally, sublingually, inhalationally, intramuscularly, subcutaneously, etc).

[0095] In some preferred embodiments, the oral dosage form contains: (i) an orally therapeutically effective amount of the cannabinoid agonist and (ii) an opioid antagonist which is present in a substantially releasable form (e.g., is co-released with the cannabinoid agonist into the gastrointestinal tract following disintegration and diffusion or dissolution of the oral dosage form), wherein the dosage form provides a desired therapeutic effect without precipitating signs and symptoms of cannabinoid agonist or opioid agonist withdrawal under conditions of normal use, but can precipitate signs and symptoms of cannabinoid agonist or opioid agonist withdrawal under conditions of abuse, misuse or overdose by the oral or non-oral route of administration.

[0096] In some preferred embodiments, the oral dosage form contains: (i) an orally therapeutically effective amount of the cannabinoid agonist and (ii) an opioid antagonist which is present in a substantially releasable form (e.g., is co-released with the cannabinoid agonist into the gastrointestinal tract following disintegration and diffusion or dissolution of the oral dosage form), wherein the dosage form provides a desired therapeutic effect without precipitating signs and symptoms of cannabinoid agonist withdrawal under conditions of normal use, but can precipitate signs and symptoms of opioid agonist withdrawal under conditions of normal use in individuals who are taking opioids (e.g., surreptitious or undeclared opioid use in a polydrug abuser masquerading as a patient requiring a cannabinoid agonist for a legitimate medical use).

[0097] In some embodiments, the oral dosage form of the present invention is directed to an oral dosage form comprising (i) a cannabinoid agonist in releasable form and (ii) an opioid antagonist which is in a substantially releasable form, wherein the agonist and antagonist are isolated from each other in two or more distinct layers.

[0098] In some embodiments, the oral dosage form of the present invention is directed to an oral dosage form comprising (i) a cannabinoid agonist in releasable form and (ii) an opioid antagonist which is in a substantially

releasable form, wherein the agonist and antagonist are at least partially interdispersed.

[0099] In some embodiments, the oral dosage form of the present invention is directed to an oral dosage form comprising (i) a cannabinoid agonist in releasable form and (ii) an opioid antagonist which is in a substantially releasable form, wherein the cannabinoid agonist and opioid antagonist are interdispersed and visually indistinguishable.

[00100] In some embodiments, the oral dosage form of the present invention is directed to an oral dosage form comprising (i) a cannabinoid agonist in releasable form and (ii) an opioid antagonist which is in a substantially releasable form, wherein the cannabinoid agonist and opioid antagonist are interdispersed and indistinguishable on the basis of physical characteristics, including bead diameter, density, texture, smell, solvent extractability or flotation.

[00101] In certain embodiments, the oral dosage form optionally contains abuse intervention agent(s), in sequestered, partially sequestered, unsequestered, non-releasable, partially releasable or releasable form. In certain embodiments, the abuse intervention agent(s) is not aversive when administered orally at therapeutic doses but is aversive orally when administered in excess (e.g. under conditions of abuse, misuse, excess intake, etc.), is aversive when administered at therapeutic or excessive doses by a non-oral route (e.g. intranasally, parenterally, inhalationally, etc).

[00102] In certain embodiments, the oral dosage form comprising (i) a cannabinoid agonist in releasable form and (ii) an opioid antagonist which is in a substantially releasable form, contains other substances which make extraction of the cannabinoid agonist difficult (e.g. gelling agents).

[00103] The invention is also directed to a method of treating or preventing diseases and disorders amenable to treatment with cannabinoid agonists with the dosage forms disclosed herein. The method can comprise providing an oral dosage form containing a cannabinoid agonist in a releasable form and an

opioid antagonist in substantially releasable form; and orally administering the intact oral dosage form.

[00104] The amount of opioid antagonist required to achieve the objectives of the invention will vary between opioid antagonists, but can be determined based on the physicochemical, pharmaceutical, pharmacokinetic and pharmacologic properties and upon testing of the drug, including its solubility, molecular weight, bioavailability by the oral and non-oral routes, half life, intrinsic clearance, potency, absolute bioavailability, abuse nullifying effects, and the like. The amount of opioid antagonist required to achieve the objectives of the invention will also depend, among other things on the amount of opioid agonist consumed by the user or drug abuser, the timing of such use or abuse, the pharmacologic tolerance of the drug user or abuser to opioid agonist and idiosyncatrtic variable.

[00105] It reasons that "opioid experienced" individuals who are tolerant to the effects of opioid agonists will generally tend to abuse larger quantities of opioid agonists than "opioid inexperienced" or "opioid naïve" individuals. Therefore, depending on a number of physiologic, pathophysiologic and pharmacologic factors, the nullification effects of the opioid antagonist of the dosage form will range from mild attenuation to complete blockade of the mood altering effects of the co-abused opioid agonist, the tampered dosage form generally producing effects more robust than the intact dosage form within the same patient. Depending on the half-life of the used or abused opioid agonist and the opioid antagonist of the dosage form, the abuse nullifying effects of the opioid antagonist may be shorter than the duration of action of the opioid agonist (in which case there may be a resurgence of mood altering effects) or longer that the duration of the opioid agonist (in which case, there may be a complete termination of effects and also possible blockade of the effects of additional doses of opioid agonist consumed within minutes, hours or days of the abuse of the dosage form of the invention).

[00106] The selection of opioid antagonist for use with the dosage form of the invention will also depend on other factors. For example, a potent opioid

antagonist will require a smaller amount within the dosage form, which is generally an advantage. Some opioid antagonists, such as naloxone are significantly more effective in reversing opioid agonist effects when given parenterally than when given orally, due to a high first pass effect. Upon tampering, such opioid antagonists are more likely to act as a deterrent when administered non-orally (e.g., intravenously) than when consumed by the oral route. One way to make such an opioid antagonist equally deterring is to increase the amount of the opioid antagonist in the dosage form, such that following tampering and oral administration, it "overwhelms" the presystemic barriers to bioavailability (e.g., the hepatocytes), and some component of the ingested drug bypasses first pass metabolism.

[00107] Alternatively, opioid antagonists such as naltrexone are bioavailable by the oral route may be used. When included in the dosage form of the invention, it effectively reverses opioid agonist effects upon oral ingestion and also upon non-oral administration (e.g., intanasally, inhalationally, intravenously, etc). Yet other opioid antagonists such as methylnaltrexone or alvimopan are considered to be peripherally restricted opioid antagonists. Such opioid antagonists tend to have difficulty crossing into the CNS, and depending on the dose, substantially exert their effects on peripheral opioid receptors. When contained in dosage forms of the present invention and upon application to intact skin or tampering, peripherally restricted opioid antagonists are effective against peripheral opioid agonist effects when given by the non-oral (e.g., intravenous and inhalational route) but may not be or may be less effective as abuse deterrents when the dosage form is orally ingested. In many cases, peripherally restricted opioid antagonists can overwhelm the CNS when given in large quantities.

[00108] In preferred embodiments, the present invention is directed to oral dosage forms having reduced potential for abuse, misuse, diversion and toxicity upon abuse, misuse or tampering, without diminishing the therapeutic or beneficial effects of the dosage form.

[00109] In preferred embodiments, the dosage form contains a therapeutically effective amount of the cannabinoid agonist, the oral dosage form providing a desired therapeutic effect. Because the opioid antagonist is present in a substantially releasable form, it substantially blocks the therapeutic effects of co-abused or co-used opioid agonists when the dosage form is administered intact, and further, blocks the effect of co-abused opioid agonist if tampered with, followed by ingestion, injection, insufflation or inhalation.

[00110] Recently, a buccal spray containing THC and cannabidiol (Sativex™) was approved in Canada for the symptomatic relief of neuropathic pain in multiple sclerosis. The prescribing information warns physicians that the drug *"should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence. Multiple substance abuse is common and marijuana, which contains the same active compounds, is a frequently abused substance. Therefore, SATIVEX® is not recommended in patients with addiction and drug abuse liability."* The prescribing information states about the following effects: *"Following mild THC intoxication, symptoms include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following moderate THC intoxication, symptoms include memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following severe THC intoxication, symptoms include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders."*

[00111] The invention is also directed to a method of treating or preventing diseases and disorders amenable to treatment with a cannabinoid agonist.

[00112] The invention is also directed to a method of treating or preventing Alzheimer's disease, schizophrenia, depression, alcoholism, Parkinson's disease, stroke, premature labor, endotoxic shock, hepatic cirrhosis, atherosclerosis, cancer, glaucoma, emesis, multiple sclerosis, amyotrophic lateral sclerosis, encephalitis, Huntington's disease, obesity, memory

impairment, cognitive impairment, hypertension, cardiogenic shock, cerebral ischemia, myocardial infarction, neurotoxicity, febrile seizures, pruritus of various etiology and various intestinal disorders with the dosage forms disclosed herein.

[00113] Another embodiment of the invention is directed to a method of preventing or treating diseases and disorders amenable to treatment with a cannabinoid agonist, comprising providing an oral dosage form containing a releasable form of a cannabinoid agonist and a substantially releasable form of a opioid antagonist; and orally administering the dosage form to provide: (i) plasma levels of cannabinoid agonist greater than the minimum therapeutic concentration and one or more of the following, (ii) when the dosage form is administered intact orally, plasma levels of opioid antagonist sufficient to deter use or abuse of opioid agonists; (iii) when the dosage form is administered intact orally at excessive dose (e.g., overdose or oral drug abuse), plasma levels of opioid antagonist sufficient to deter use or abuse of opioid agonists; (iii) when the dosage form is administered by the non-oral route (e.g., intranasal, inhalational, intravenous), plasma levels of opioid antagonist sufficient to deter use or abuse of opioid agonists, but plasma levels of opioid antagonist that would have been insufficient to deter use or abuse of opioid agonists if the dosage form had been consumed orally; (iv) when the dosage form is administered intact orally, plasma levels of opioid antagonist insufficient to deter use or abuse of opioid agonists in opioid agonist naïve or opioid agonist inexperienced subjects, but sufficient to deter use or abuse of opioid agonists in subjects who are opioid experienced and opioid tolerant; (v) when the dosage form is administered tampered (e.g., intranasal, inhalational, intravenous routes), plasma levels of opioid antagonist sufficient to deter use or abuse of opioid agonists; (vi) when the dosage form is administered intact, plasma levels of opioid antagonist sufficient to deter use or abuse of opioid agonists, and further, when the dosage form is administered tampered (e.g., intranasal, inhalational, intravenous routes, or crushing an a controlled release dosage form followed by oral ingestion), plasma levels of opioid antagonist

providing a greater amount of deterrence to the use or abuse of opioid agonists.

[00114] Another embodiment of the invention is directed to a method of preventing or treating pain with the disclosed dosage forms. In certain embodiments, the method of treating pain in patients with a dosage form having less abuse potential comprises providing an oral dosage form containing a releasable form of a cannabinoid agonist and a substantially releasable form of a opioid antagonist; and orally administering the oral dosage form.

[00115] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of a opioid antagonist, wherein (i) the cannabinoid agonist and opioid antagonist are interdispersed and are not isolated from each other in two distinct layers; (ii) the dosage form is in the form of multiparticulates individually coated with the cannabinoid agonist or opioid antagonist; (iii) the dosage form is in the form of multiparticulates, each multiparticulate coated with the cannabinoid agonist plus the opioid antagonist; (iv) the dosage form is in the form of inert or sugar beads, individually coated with the cannabinoid agonist or the opioid antagonist; (v) the dosage form is in the form of inert or sugar beads, each coated with the cannabinoid agonist plus the opioid antagonist; (vi) wherein the cannabinoid agonist and opioid antagonist are isolated from each other in two or more distinct layers; (vii) wherein the cannabinoid agonist plus the opioid antagonist are dispersed in the same matrix; (viii) wherein the cannabinoid agonist and the opioid antagonist are dispersed in the different matrices, interdispersed and the filled into uncompressed capsules or compressed tablets; (ix) the cannabinoid agonist and opioid antagonist are isolated from each other in two or more distinct layers; (x) the cannabinoid agonist and opioid antagonist are granulated separately and optionally blended together before capsule filling or tablet compression; (xi) the cannabinoid agonist multiparticulates or beads are overcoated with the opioid antagonist and the optionally overcoated with one

or more coats comprising aqueous or organic film or polymeric coat to provide an immediate release form, a controlled release form or a mixture of immediate release and controlled release forms; (xii) the opioid antagonist multiparticulates or beads are overcoated with the cannabinoid agonist and the optionally overcoated with one or more coats comprising aqueous or organic film or polymeric coat to provide an immediate release form, a controlled release form or a mixture of immediate release and controlled release forms; (xiii) the dosage form comprises multiparticulate matrices or beads containing the cannabinoid agonist or the opioid antagonist; and /or (xiv) the dosage form comprises one or more populations of multiparticulate matrices or beads containing the cannabinoid agonist or the opioid antagonist.

[00116] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of a opioid antagonist, wherein (i) the cannabinoid agonist plus the opioid antagonist are dispersed within a matrix; (ii) the matrix is encapsulated; (iii) the dosage form is in the form of multiparticulates, or multiparticulates dispersed in a matrix and contained in a capsule, or multiparticulates dispersed in a matrix and compressed into a tablet; (iv) the dosage form comprises a matrix that is in the form of pellets or coated beads; (v) the dosage form comprises a compressed tablet, compressed capsule or uncompressed capsule; (vi) the dosage form comprises a liquid fill capsule; and/or (vi) an enteric coating.

[00117] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of a opioid antagonist, wherein the dosage form is an osmotic dosage form which comprises a single layer or bilayer core comprising cannabinoid agonist and opioid antagonist or a pharmaceutically acceptable salt thereof; an expandable polymer; a semipermeable membrane surrounding the core; and a passageway disposed in the semipermeable membrane for sustained release of the cannabinoid agonist and opioid antagonist or a pharmaceutically acceptable salt thereof.

[00118] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of a opioid antagonist, wherein the dosage form is an osmotic dosage form which comprises a single layer or bilayer core comprising cannabinoid agonist or a pharmaceutically acceptable salt thereof; an expandable polymer; a semipermeable membrane surrounding the core; and a passageway disposed in the semipermeable membrane for sustained release of the cannabinoid agonist or a pharmaceutically acceptable salt thereof; an overcoating of the opioid antagonist for immediate release of the opioid antagonist or a pharmaceutically acceptable salt thereof.

[00119] In some preferred embodiments, the dosage form provides an oral dosage form for the treatment of pain or other diseases, disorders or symptoms amenable to treatment with a cannabinoid agonist comprising (i) a drug layer comprising an effective amount of cannabinoid agonist and opioid antagonist or pharmaceutically acceptable salts or mixtures thereof; and (ii) a displacement layer comprising an osmopolymer; and (b) a semipermeable wall surrounding the bilayer core having a passageway disposed therein for the release of said cannabinoid agonist and opioid antagonist or pharmaceutically acceptable salts or mixtures thereof; said dosage form suitable for extended release oral administration to a human patient.

[00120] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist comprising a matrix, said matrix is a plurality of multiparticulate matrices. In some preferred embodiments, the multiparticulates are compressed into a tablet. In some preferred embodiments, the multiparticulates are disposed in a pharmaceutically acceptable capsule.

[00121] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist in a reservoir comprising: (i) cannabinoid agonist and opioid antagonist; (ii) a membrane layer, said

membrane being substantially permeable to cannabinoid agonist and opioid antagonist; wherein the dosage form substantially releases the cannabinoid agonist and opioid antagonist from the dosage form to render said dosage form suitable for extended release to a human patient.

[00122] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist comprising a plurality of pharmaceutically acceptable beads coated with an effective amount of cannabinoid agonist and opioid antagonist; and overcoated with controlled release material to render said dosage form suitable for extended release oral administration to a human patient.

[00123] In some preferred embodiments, the oral dosage form comprises a plurality of pharmaceutically acceptable beads coated with cannabinoid agonist and/or opioid antagonist and overcoated with controlled release material.

[00124] In some preferred embodiments, the controlled release material of the oral dosage form of the invention is selected from the group consisting of hydrophobic polymers, hydrophilic polymers, gums, protein derived materials, waxes, shellac, oils and mixtures thereof.

[00125] In some preferred embodiments, the controlled release material of the oral dosage form of the invention is selected from the group consisting of hydrogenated Type I or Type II vegetable oils, polyoxyethylene stearates and distearates, glycerol monostearate, and non-polymeric, non-water soluble liquids carbohydrate-based substances or poorly water soluble, high melting point (mp = 40 to 100° C) waxes and mixtures thereof.

[00126] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist, wherein said cannabinoid agonist and opioid antagonist are in immediate release form.

[00127] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially

releasable form of an opioid antagonist, wherein said cannabinoid agonist and/or said opioid antagonist are in pulsatile release form.

[00128] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist, wherein said cannabinoid agonist and opioid antagonist are in controlled release form.

[00129] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of a opioid antagonist, wherein said cannabinoid agonist and opioid antagonist are in immediate release and controlled release form.

[00130] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist, wherein said cannabinoid agonist is in immediate release form and said opioid antagonist is in controlled release form.

[00131] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist, wherein said cannabinoid agonist is in controlled release form and said opioid antagonist is in immediate release form.

[00132] Another embodiment of the invention is directed to an oral dosage form comprising a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist, wherein said cannabinoid agonist and opioid antagonist both provide gastrointestinal release over an extended period of time when administered to patients. In other embodiments of the invention, said cannabinoid agonist provides gastrointestinal release over an extended period of time and said opioid antagonist is provides gastrointestinal release over a short period of time. In yet other embodiments of the invention, said opioid antagonist provides gastrointestinal release over an extended period of time and said cannabinoid agonist is provides gastrointestinal release over a short period of time. In yet other embodiments of the invention, said

cannabinoid agonist provides short lived or sustained effective plasma concentrations, while said opioid antagonist is provides undetectable or negligible plasma concentrations due to poor oral absorption, inadequate oral absorption, low oral bioavailability, high pre-systemic clearance, high intrinsic clearance or high first pass effect, said dosage form providing abuse deterrence upon excess oral consumption or upon tampering followed by parenteral, intranasal or inhalational routes of administration.

[00133] In some preferred embodiments, the in vivo pharmacokinetic parameters of the specifications and claims are derived or determined under fed conditions. In other preferred embodiments, the in vivo pharmacokinetic parameters are derived or determined under fasted conditions.

[00134] Some or all of the above objects and others are achieved by embodiments of the present invention, which is directed in part to a dosage form of a releasable form of a cannabinoid agonist and a substantially releasable form of a opioid antagonist.

[00135] The invention is also directed to kits of the dosage forms disclosed herein.

[00136] All kinds of kits of the present invention are contemplated. In some preferred embodiments, also provided are kits for use in treating or preventing a medical condition amenable to prevention or treatment with a cannabinoid agonist, including pain with an oral dosage form of releasable cannabinoid agonist and substantially releasable opioid antagonist, or pharmaceutically acceptable salts thereof or mixtures thereof for a subject in need of such prevention or treatment, comprising: (i) a dosage form of the invention; (ii) a container for the dosage form; and optionally, any of (iii) to (vi): (iii) a container for individual units of the dosage form (e.g., individual tablets or capsules in blisters); (iv) educational instructions in any media about various medical conditions, their etiology, pathophysiology, consequences and treatment, including information on the potential for abuse and diversion and methods for prevention of same and information on the proper use and disposal of the medication; (v) containers or bags for the safe disposal of any

used or remaining unused dosage form, preferably child proof and flushable; (vi) tamper evident and child proof packaging for the kit and its contents.

[00137] In another aspect, the invention relates to a method for resisting or deterring abuse, misuse, overdose and toxicity, comprising oral administration of a dosage form containing a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist.

[00138] In another aspect, the invention relates to a method for resisting or deterring abuse, misuse, overdose and toxicity in polydrug abusers, comprising oral administration of a dosage form containing a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist.

[00139] In another aspect, the invention relates to a method for resisting or deterring abuse, misuse, overdose and toxicity in opioid abusers, comprising oral administration of a dosage form containing a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist.

[00140] In another aspect, the invention relates to a method for reducing the illegal diversion of the dosage form into the illicit market, comprising oral administration of a dosage form containing a releasable form of a cannabinoid agonist and a substantially releasable form of an opioid antagonist.

[00141] In some embodiments, the dosage form of the invention has a dosing frequency of up to every 0.5, 1, 2, 4, 6, 8, 12, 24 or 48 hours. In a preferred embodiment, said dosing frequency is every 6, 8, 12 or 24 hours. In particularly preferred embodiments, said dosing frequency is every 12 or 24 hours.

[00142] In some embodiments, the cannabinoid agonist of the dosage form has a duration of effect of up to 0.5, 1, 2, 4, 6, 8, 12, 24 or 48 hours. In a preferred embodiment, said duration of effect is 6, 8, 12 or 24 hours. In particularly preferred embodiments, said duration of effect is 12 or 24 hours.

[00143] In certain embodiments of the invention, when the intact dosage form upon ingestion or immersion in a solvent for a period of time substantially

continuously provides a release rate ratio of the opioid antagonist to the cannabinoid agonist of about 0.001:1 to about 1000:1, about 0.005:1 to about 200:1; about 0.01:1 to about 100:1; about 0.05:1 to about 20:1; about 0.1:1 to about 10:1; about 0.5:1 to about 2:1, about 1:1 to about 1000:1; about 2:1 to about 100:1; about 5:1 to about 50:1, about 10:1 to about 100:1; about 2:1 to about 10:1; about 1:1 to about 20:1, about 2:1 to about 15:1; about 2:1 to about 40:1; and about 2:1 to about 4:1, wherein the period of time of immersion is up to about 1 minute to about 24 hours.

**[00144]** In some embodiments, when the dosage form of the invention comprising a releasable cannabinoid agonist and a substantially releasable opioid antagonist is intentionally or accidentally used in the setting of opioid agonist use, opioid agonist abuse, or cannabinoid abuse, the substantially releasable opioid antagonist reduces or nullifying the "high", "liking", pleasurable, euphoric, calming, anxiolytic, relaxing, psychotomimetic, mood altering, rewarding, or reinforcing effects of the opioid agonist or the cannabinoid agonist without: (i) increasing the therapeutic or analgesic effects of the cannabinoid agonist; or (ii) decreasing the therapeutic or analgesic effects of the cannabinoid agonist.

**[00145]** In some embodiments, when the dosage form of the invention comprising a releasable cannabinoid agonist and a substantially releasable opioid antagonist is intentionally or accidentally used in the setting of opioid agonist use or opioid agonist abuse, the substantially releasable opioid antagonist precipitates signs and symptoms of opioid agonist withdrawal or an opioid abstinence syndrome.

**[00146]** In some embodiments, when the dosage form of the invention comprising a releasable cannabinoid agonist and a substantially releasable opioid antagonist is used in conjunction with opioid agonists, the substantially releasable opioid antagonist precipitates signs and symptoms of opioid agonist withdrawal only in individuals who are tolerant to opioid agonists, who are habitual users of opioid agonists or who use large amounts of opioid agonists, said dosage form not aversive in individuals who are not tolerant to opioid

agonists, or who are not habitual users of opioid agonists or who do not use large amounts of opioid agonists.

[00147] In some embodiments, when the dosage form of the invention comprising a releasable cannabinoid agonist and a substantially releasable opioid antagonist is used in conjunction with opioid agonists, the substantially releasable opioid antagonist reduces or nullifying the "high", "liking", pleasurable, euphoric, calming, anxiolytic, relaxing, psychotomimetic, mood altering, rewarding, or reinforcing effects only in individuals who are tolerant to opioid agonists, who are habitual users of opioid agonists or who use large amounts of opioid agonists, said dosage form not aversive in individuals who are not tolerant to opioid agonists, or who are not habitual users of opioid agonists or who do not use large amounts of opioid agonists.

[00148] In some embodiments, when the dosage form of the invention comprising a releasable cannabinoid agonist and a substantially releasable opioid antagonist is used in conjunction with opioid agonists, the substantially releasable opioid antagonist precipitates signs and symptoms of opioid agonist withdrawal only in individuals who administer the tampered dosage form by the intravenous, inhalational or intranasal route, said dosage form not aversive in individuals who take the dosage form by the oral route at medically appropriate doses.

[00149] In some embodiments, when the dosage form of the invention comprising a releasable cannabinoid agonist and a substantially releasable opioid antagonist is used in conjunction with opioid agonists, the substantially releasable opioid antagonist reduces or nullifying the "high", "liking", pleasurable, euphoric, calming, anxiolytic, relaxing, psychotomimetic, mood altering, rewarding, or reinforcing effects only individuals who administer the tampered dosage form by the intravenous, inhalational or intranasal route, said dosage form not aversive in individuals who take the dosage form by the oral route at medically appropriate doses.

[00150] The invention is also directed to methods of preparing the dosage forms disclosed herein. In certain embodiments, the invention comprises a

method of preparing an oral dosage form comprising a releasable cannabinoid agonist and a substantially releasable opioid antagonist. In certain embodiments, the invention comprises a method of preparing an oral dosage form comprising a releasable cannabinoid agonist and a releasable opioid antagonist.

[00151] In some embodiments, some or all of the embodiments of the dosage form comprising a releasable cannabinoid agonist and a substantially releasable opioid antagonist can also be achieved with a releasable cannabinoid agonist and a releasable opioid antagonist.

[00152] In some embodiments, some or all of the embodiments of the dosage form comprise a releasable cannabinoid agonist and a releasable opioid antagonist.

[00153] The term "analgesic effectiveness" is defined for purposes of the present invention as a satisfactory prevention, reduction in or elimination of pain, along with a tolerable level of side effects, as determined by the human patient. The term "therapeutic effectiveness" is defined for purposes of the present invention as a satisfactory prevention or treatment of diseases and disorders amenable to treatment with a cannabinoid agonist, including their signs and symptoms, along with a tolerable level of side effects, as determined by the human patient.

[00154] The term "an opioid antagonist in a substantially releasable form" refers to an opioid antagonist that is released or substantially released into the gastrointestinal tract after oral administration, regardless of the amount of opioid antagonist absorbed into the systemic circulation after such oral use. Opioid antagonists of varying absolute oral bioavailabilities are contemplated, from those which have no or negligible oral bioavailability to those with high oral bioavailability. Differences in bioavailability of the opioid antagonist may be for any reason, including differences in pre-hepatic, hepatic and extrahepatic clearance, differences in intrinsic hepatic clearance, differences in gastrointestinal absorption and the like.

[00155] The term "at least partially blocking the cannabinoid agonist effect", "blocking the cannabinoid agonist effect" "nullifying the cannabinoid agonist effect" and the like are defined for purposes of the present invention to mean that the opioid antagonist at least significantly blocks the "high", "liking", pleasurable, euphoric, calming, anxiolytic, auditory and visual perceptual alterations, relaxing, psychotomimetic, rewarding or reinforcing effects of the cannabinoid agonist, thereby reducing the potential for abuse of the cannabinoid agonist in the dosage form. The term "at least partially blocking the cannabinoid agonist effect", "blocking the cannabinoid agonist effect" "nullifying the cannabinoid agonist effect" and the like also means capable of precipitating a cannabinoid agonist withdrawal or abstinence syndrome in individuals who are have a tolerance to or are physically dependent on cannabinoid agonists.

[00156] The term "at least partially blocking the opioid agonist effect", "blocking the opioid agonist effect" or "nullifying the opioid effect" and the like are defined for purposes of the present invention to mean that the opioid antagonist at least significantly blocks the "high", "liking", pleasurable, euphoric, calming, anxiolytic, mood altering, relaxing, psychotomimetic, rewarding or reinforcing effects of the opioid agonist when it is co-administered with the cannabinoid agonist (e.g., in the setting of poly-drug abuse), thereby reducing the potential for abuse of the cannabinoid agonist in polydrug abuse individuals. The term "at least partially blocking the opioid agonist effect", "blocking the opioid agonist effect" or "nullifying the opioid effect" and the like also means capable of precipitating an opioid agonist withdrawal or abstinence syndrome in individuals who are have a tolerance to or are physically dependent on opioid agonists.

[00157] The term "particles" of opioid antagonist and cannabinoid agonist, as used herein, refers to granules, spheroids, beads or pellets comprising the opioid antagonist. In certain preferred embodiments, the opioid antagonist particles are about 0.2 to about 2 mm in diameter, more preferably about 0.5 to about 2 mm in diameter.

[00158] In certain embodiments of the present invention, the ratio of the cannabinoid agonist and the opioid antagonist, present in a substantially non-releasable form, is about 1:10,000 to about 10,000:1 or about 1:1000 to about 1000:1 by weight, preferably about 1:100 to about 100:1 by weight, and more preferably about 10:1 to 1:10 by weight.

[00159] In certain embodiments, a combination of two cannabinoid agonists is included in the dosage form with the opioid antagonist. In further embodiments, one or more cannabinoid agonist and a opioid antagonist is included and a further non-cannabinoid drug is also included for the treatment of the same medical condition as the cannabinoid agonist or for the treatment of a different medical condition. In certain embodiments, a combination of two opioid antagonists is included in the dosage form with the cannabinoid agonist(s).

[00160] The term "cannabinoid agonist" means a substance that binds to one or more cannabinoid receptor to exert an agonist or partial agonist effect.

[00161] An "agonist" is a ligand that binds to a receptor and alters the receptor state resulting in a biological response. Conventional agonists increase receptor activity, whereas inverse agonists reduce it (See Neubig et al, IUPHAR Committee on Receptor Nomenclature and Classification, Pharmacol Rev, 2003; Howlett et al., Mol Pharmacol, 1988).

[00162] The term "cannabinoid antagonist" means an antagonist substance or an inverse agonist that binds to one or more cannabinoid receptor to exert an antagonist effect.

[00163] An "antagonist" is a drug or ligand that reduces the action of another drug or ligand, generally an agonist. Many antagonists act at the same receptor macromolecule as the agonist. (See Neubig et al, IUPHAR Committee on Receptor Nomenclature and Classification, Pharmacol Rev, 2003; Howlett et al., Mol Pharmacol, 1988).

[00164] The term "cannabinoid receptor" means a molecule that causes a specific physiologic, pathophysiologic or pharmacologic effect after binding to $CB_1$, $CB_2$, non-$CB_1$/$CB_2$ cannabinoid sites, $TRPV_1$ receptors, as well as

other G protein-coupled receptors (GPCRs) that form part of the endocannabinoid system (Wiley and Martin, Chemistry Physics of Lipids, 2002; Begg et al., Pharmacol Ther, 2005; Howlett et al., Neuropharmacol, 2004; Pertwee, AAPS Journal, 2005; International Union of Pharmacology (IUPHAR) Receptor Database; Howlett et al., Mol Pharmacol, 1988).

[00165] The term "receptor" means a molecule within a cell, on a cell surface, on a membrane, in tissue, in fluid or otherwise found in humans that serves as a recognition or binding site to cause specific physiologic, pathophysiologic or pharmacologic effects. The term "receptor" also means a cellular macromolecule, or an assembly of macromolecules, that is concerned directly and specifically in chemical signaling between and within cells. Combination of a hormone, neurotransmitter, drug, ligand, or intracellular messenger with its receptor(s) initiates a change in cell function (Neubig et al, IUPHAR Committee on Receptor Nomenclature and Classification, Pharmacol Rev, 2003).

[00166] The term "tampering" or "tamper" means any manipulation including by mechanical, thermal and/or chemical means which changes the physical properties of the dosage form, e.g., to liberate the cannabinoid agonist for immediate release if it is in sustained release form, or to make the cannabinoid agonist available for inappropriate use such as administration by an alternate route, e.g., parenterally inhalationally, intranasally. The tampering can be, e.g., by means of crushing, shearing, grinding, chewing, dissolution in a solvent, heating (e.g., greater than about 45.degree. C.), mechanical extraction, solvent extraction, solvent immersion, combustion, or any combination thereof.

[00167] The term "abuse", "misuse", "cannabinoid abuse", "cannabinoid agonist abuse", "cannabinoid agonist misuse", "opioid agonist abuse", "opioid agonist misuse" or "opioid abuse" with respect to the dosage form of the invention and opioid agonists used outside or separate from the dosage form, means single use, intermittent use, repeated use, recreational use and chronic use of the specified abusable drug or class of abusable drugs: (i) in quantities or by methods and routes of administration that do not conform to standard

medical practice; (ii) outside the scope of specific instructions for use provided by a qualified medical professional; (iii) outside the supervision of a qualified medical professional; (iv) outside the approved instructions on proper use provided by the drug's legal manufacturer; (v) which is not in specifically approved dosage forms for medical use as pharmaceutical agents; (vi) where there is an intense desire for and efforts to procure same; (vii) compulsive use; (viii) through acquisition by manipulation of the medical system, including falsification of medical history, symptom intensity, disease severity, patient identity, doctor shopping, prescription forgeries; (ix) where there is impaired control over use; (x) despite harm; (xi) by procurement from non-medical sources; (xii) by others through sale or diversion by the individual into the non-medical supply chain; (xiii) for medically unapproved or unintended mood altering purposes.

[00168] The term "mood altering" is defined for purposes of the present invention to mean that the "high", "liking", pleasurable, euphoric, calming, anxiolytic, auditory and visual perceptual alterations, relaxing, psychotomimetic, mood altering, rewarding, reinforcing alterations in perception, cognition and mental focus; sexual gratification; sexual arousal; sexual desire and sexual anticipation; increased socialization effects of the abusable drug.

[00169] The term "abuse resistant", "abuse deterrent", "tamper resistant", "deter abuse" ", "deter misuse", resist abuse" and "resist misuse" and "deter abuse" (as well of the words "resist" or "deter" when applied to abusable drugs of the invention) are used interchangeably in the context of the present invention and include pharmaceutical compositions and methods that resist, deter, discourage, diminish, delay and/or frustrate: (i) the intentional, unintentional or accidental physical, chemical or thermal manipulation or tampering of the dosage form (e.g., crushing, shearing, grinding, chewing, dissolving, tearing, puncturing, melting, needle aspiration, combustion, smoking, inhalation, insufflation, extraction by mechanical, thermal and chemical means, and/or filtration); (ii) the intentional, unintentional or

accidental use or misuse of the dosage form outside the scope of specific instructions for use provided by a qualified medical professional, outside the supervision of a qualified medical professional and outside the approved instructions on proper use provided by the drug's legal manufacturer (e.g., intravenous use, intranasal use, inhalational use and oral ingestion to provide high peak concentrations); (iii) the intentional, unintentional or accidental conversion of a controlled release dosage form of the invention into a more immediate release form; (iv) the intentional and iatrogenic increase in physical and psychic effects sought by recreational drug users, addicts, and patients with pain who have an addiction disorder; (v) attempts at surreptitious administration of the dosage form to a third party (e.g., in a beverage); (vi) attempts to procure the dosage form by manipulation of the medical system and from non-medical sources; (vii) the sale or diversion of the dosage form into the non-medical supply chain and for medically unapproved or unintended mood altering purposes; (viii) the intentional, unintentional or accidental attempts at otherwise changing the physical, pharmaceutical, pharmacological and/or medical properties of the dosage form from what was intended by the manufacturer.

[00170] As used herein, the term "aversive agents", "aversion producing agents" and "aversive compounds" and "aversive" in reference to the effects produced by opioid antagonists or abuse intervention agents refers to opioid agonists and means compounds contained within the dosage form that produce an aversive, undesirable, repugnant, distasteful, unpleasant, unacceptable physiologic or unacceptable psychic effects, or that pharmacologically block or reduce one or more of the following effects: mood alterations; euphoria, pleasure; a feeling of high; a feeling of drug liking; anxiolysis; sedation; calmness; a state of relaxation; psychotomimesis; hallucinations; alterations in perception, cognition and mental focus; hypersomnia; sexual gratification; sexual arousal; sexual desire and sexual anticipation; increased socialization; social anxiety; psychologically reinforcement; and psychologically rewards.

[00171] The term "sustained release" is defined for purposes of the present invention as the release of the cannabinoid agonist from the oral dosage form at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective concentration) but below toxic levels over a period of 4 to 24 hours, preferably over a period of time indicative of a twice-a-day or a once-a-day formulation. As used herein, "sustained release" is interchangeable with "extended release", "controlled release", "modified release", "delayed release" and the like.

[00172] The term "subject" for purposes of treatment is used interchangeably with "patient", "male", "female", and includes any human who has a medical condition amenable to prevention or treatment with a cannabinoid agonist.

[00173] The terms "medical condition", "malady", "disease", "disorder" and "pathological states" are used interchangeably and are intended to have their broadest interpretation to refer to any physiologic, pathologic or pathophysiologic state in a human that can be prevented, treated, managed or altered to produce a desired, usually beneficial effect.

[00174] "Drug", "drug substance", "substance", "therapeutic agent", "pharmacological agent", "pharmaceutical agent", "active agent" and "agent" are used interchangeably and are intended to have their broadest interpretation as to any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial effect. In general, this includes therapeutic agents in all of the major therapeutic areas.

[00175] "Pharmaceutically or therapeutically acceptable excipient or carrier" refers to a solid or liquid filler, diluent or encapsulating substance which does not interfere with the effectiveness or the biological activity of the cannabinoid agonist and which is not toxic to the hosts, which may be either humans or animals, to which it is administered.

[00176] The term "pharmaceutically acceptable salt" as used herein refers to a salt which is toxicologically safe for human and animal administration. Nonlimiting examples of salts include hydrochlorides, hydrobromides, hydroiodides, sulfates, bisulfates, nitrates, citrates, tartrates, bitartrates,

phosphates, malates, maleates, napsylates, fumarates, succinates, acetates, terephlhalates, pamoates and pectinates.

[00177] Mammalian tissues express at least two cannabinoid receptors, both of which are G-protein coupled. These are $CB_1$ receptors and $CB_2$ receptors. $CB_1$ receptors are expressed are primarily expressed in peripheral and central nerve terminals where they mediate inhibition of neurotransmitter release. In the CNS, especially high levels of $CB_1$ receptors are found in the cerebellum, hippocampus and basal ganglia. $CB_2$ receptors are found primarily on immune and hematopoietic cells outside (and also within) the central nervous system, where they appear to modulate cytokine release and immune cell migration. Studies using $CB_1$ and $CB_2$ receptor knockout mice indicate that some of the effects of endocannabinoids are not mediated by either $CB_1$ or $CB_2$ receptors, suggesting the existence of additional yet to be identified sites of action. Some cannabinoid effects resist classification as either $CB_1$ and $CB_2$-mediated. There is growing evidence suggesting the involvement of additional receptors, which include $TRPV_1$ receptors and at least 2 G protein-coupled receptors (GPCRs) of unclear molecular identity that have only been defined pharmacologically.

[00178] The human cannabinoid system is involved in a number of pathological states, including Alzheimer's disease, schizophrenia, depression, alcoholism, Parkinson's disease, stroke, premature labor, endotoxic shock, hepatic cirrhosis, atherosclerosis, cancer, bone implantation, glaucoma, emesis and pain. Additionally, upregulation or downregulation of the endocannabinoid system is seen in a variety of animal in vivo models, including multiple sclerosis, amyotrophic lateral sclerosis, encephalitis, Alzheimer's disease, Parkinson's disease, Huntington's disease, pain, obesity, feeding, fasting, stress, memory, aging, hypertension, cirrhosis, septic shock, cardiogenic shock, cerebral ischemia, myocardial infarction, neurotoxicity, febrile seizures and various intestinal disorders.

[00179] Therefore cannabinoid receptors present a large number of potential targets for pharmacologic intervention and efforts are underway to develop

and test a variety of cannabinoid agonists and antagonists to prevent and treat various maladies. Presently, three non-specific cannabinoid receptor agonists are commercially available. Nabilone (Cesamet™) and dronabinol (Marinol™) are oral synthetic THC analogs which have been shown effective for the treatment of nausea and vomiting associated with cancer chemotherapy and AIDS-related cachexia. A buccal spray containing THC and cannabidiol (Sativex™) was approved in Canada for the symptomatic relief of neuropathic pain in multiple sclerosis and for the treatment of cancer pain.

[00180] All cannabinoid agonists are scheduled under the Controlled Substances Act of 1970. Cannabinoid agonists can produce a variety of adverse effects including a number of psychotomimetic effects such as dizziness, drowsiness, euphoria, ataxia, anxiety, disorientation, depression, hallucinations, vertigo, and psychosis. While these psychic effects are undesirable for patients, they are often sought after by recreational drug users and individuals with an addiction disorder. Cannabinoids play a modulatory role in drug seeking. They can reinstate cocaine seeking behavior after several weeks of extinction of intravenous cocaine self-administration. Similar effects have been shown in animals with a history of heroin, methamphetamine, alcohol and nicotine self-administration where cannabinoid receptor agonists have reinstated previously abolished drug seeking.

[00181] There is significant concern on the part of addiction medicine specialists and public health regulators about the potential risk of drug abuse and drug diversion with the commercialization and widespread use of new cannabinoid agonists currently in development. There is a need, therefore, for novel methods and pharmaceutical compositions to deter or preventing cannabinoid agonist abuse. There also a need for novel methods and pharmaceutical compositions to preventing cannabinoid agonist toxicity from inadvertent or intentional crushing of extended or sustained release formulations of cannabinoid agonists.

**Blunting Psychic Effects of Cannabinoid Agonists with Releasable Opioid Antagonists**

[00182] In some embodiments of the invention, the substantially releasable opioid antagonist of the dosage form has low or negligible bioavailability by the oral route. However when taken in excess by the oral route or when taken at usual or excessive doses by a non-oral route following manipulation or tampering of the dosage form (e.g., physical, chemical, thermal manipulation or solvent extraction, followed by intravenous, inhalational or intranasal administration), the opioid antagonist of the dosage form reduces or nullifies the mood altering effects of the dosage cannabinoid agonist, even when the cannabinoid agonist is the sole abused drug.

[00183] The endocannabinoid system is complex and interfaces with a number of other endogenous systems in physiologic and pathophysiologic states. One prominent system interaction for cannabinoid agonists is with the opioidergic system.

[00184] Although cannabinoid agonists and opioid agonists are distinct pharmacologic classes of drugs, they possess a similar pharmacological profile, including antinociception, catalepsy, hypothermia, motor depression, hypotension, immunosuppression, sedation and reward effects (Manzanares et al., 1999; Massi et al., 2001; Varvel et al., 2004).

[00185] In vitro studies have shown that cannabinoid agonists and opioid agonists activate mu, delta and kappa opioid, and $CB_1$, $CB_2$ and non-$CB_1$/$CB_2$ cannabinoid receptors, respectively, which are coupled to Gi/Go GTP-binding proteins that inhibit adenylyl cyclase, inhibit voltage-dependent calcium channels, stimulate potassium channels and activate the MAP kinase cascade (for review see Childers, 1991; Childers et al., 1992; Howlett, 1995).

[00186] Receptor mapping studies have shown a rather similar distribution of $CB_1$ cannabinoid and μ-opioid receptors in the dorsal horn of the spinal cord (Welch and Stevens 1992; Hohmann et al., 1999; Salio et al., 2001) and in the CNS, including the caudate, putamen, dorsal hippocampus, and substantia nigra (Mansour et al., 1988; Herkenham et al., 1991; Mailleux and Vanderhaeghen, 1992; Rodriguez et al., 2001).

[00187] Chronic use of cannabinoid agonists and opioid agonists results in pharmacologic tolerance, physical dependence and addiction. Chronic cannabinoid agonist administration induces tolerance to the antinociceptive effect of opioids (Smith et al., 1994; Welch, 1997), while chronic exposure to opioid agonists results in tolerance to the antinociceptive effect of cannabinoid agonists (Bloom and Dewey, 1978; Hine, 1985; Smith et al., 1994; Thorat and Bhargava, 1994). Cross-physical dependence between opioid agonists and cannabinoid agonists has also been demonstrated (Bhargava, 1976, 1978; Hine et al., 1975; Vela et al., 1995; Yamaguchi et al., 2001; Del Arco et al., 2002). Administration of the opioid antagonist naloxone precipitates an abstinence syndrome in cannabinoid-tolerant rats (Hirschhorn and Rosecrans, 1974; Kaymakcalan et al., 1977). Similarly, the cannabinoid antagonist SR141716A precipitates abstinence in opioid agonist dependent rats (Navarro et al., 1998). Sustained suppression of $CB_1$ receptor activity with the cannabinoid antagonist SR141716A during opioid agonist administration reduces the signs and symptoms of opioid withdrawal (Rubino et al., 2000; Mas-Nieto et al., 2001).

[00188] Cannabinoid agonists and opioid agonists seem to interact in their antinociceptive effects as illustrated by the ability of their respective antagonists to reverse cannabinoid/opioid-induced analgesia (Welch, 1993; Reche et al., 1996a,b; Cichewicz et al., 1999). The concurrent administration of opioid agonsits and cannabinoid agonists results in an enhanced antinociceptive effect, compared with either solo administartion (Cichewicz et al., 1999; Smith et al., 1998; Welch and Eads, 1999; Cichewicz and McCarthy, 2003). Administration of subanalgesic and submaximal doses of cannabinoid agonists and opioid agonists result in synergy and this effect is abolished by cannabinoid receptor and opioid receptor antagonists (Reche et al., 1996a; Smith et al., 1998; Cichewicz, 2004).

[00189] The reward process is central to the development of addiction to psychoactive drugs. A commonly used experimental method of evaluating the reinforcing properties of drugs is the self-administration test. Available data

suggest that there is an an interaction between opioids and cannabinoids with respect to reward processes. The cannabinoid antagonist SR141716A reduces self-administration of heroin (Chaperon et al., 1998; Braida et al., 2001; Mas-Nieto et al., 2001; Navarro et al., 2001; De Vries et al., 2003). The opioid antagonists naltrexone and naloxone reduce self-administration of THC (Tanda et al., 2000; Justinova et al., 2003, 2004) and the CB1 agonist CP-55,940 (Braida et al., 2001). Cannabinoid antagonists can also suppress "heroin-seeking" behavior after weeks of prior extinction (Fattore et al., 2003; Caille and Parsons, 2003; Solinas et al., 2003).

**[00190]** A majority of opioid-dependent individuals seeking treatment are polydrug abusers. The secondary illicit drug used most frequently in this population is marijuana. Prevalance estimates of marijuana use have ranged from 25% to 80% among cocaine andopiate abusers (Ball et al., 1988; Budney et al., 1996;Miller et al., 1990; Nirenberg et al., 1996; Saxon et al.,1993). Budney et al (Addiction, 1998) evaluated marijuana use among opioid abusers in patients enrolled in treatment for opioid dependence. Sixty-six per cent of participants were current marijuana users and almost all (94%) continued to use during treatment. In another study (Budney et al., Drug Abuse and Dependence, 1996) examining the relationship between marijuana use and sociodemographic, psychosocial, and drug-use variables in treatment-seeking opioid abusers, marijuana involvement was associated with less stable relationships, more frequent alcohol use, more financial difficulty, and engagement in more risky behavior including intravenous drug use and needle-sharing.

**[00191]** There is a need, therefore, for novel methods and compositions for deterring or preventing cannabinoid agonist abuse by targeting the role of opioid agonist in initiating and maintaining physical dependence, psychological dependence, tolerance and addiction to cannabinoid agonist.

**[00192]** Cannabinoid agonist abuse can be minimized by combining the releasable cannabinoid agonist with a releasable or substantially neleasable opioid antagonist in the same dosage form, such that upon use orally in excess

or upon tampering, the opioid antagonist becomes available in sufficient quantity, thereby: (i) reducing or eliminating the psychic effects of the cannabinoid agonist desired by drug addicts and recreational drug users; and (ii) reducing or eliminating the toxic effects of the cannabinoid agonist in patients who have inadvertently tampered the dosage form and in drug addicts and recreational drug users.

**Blunting Psychic Effects of Co-abused Opioid Agonists Among Cannabinoid Agonist Users and Abusers with Releaseable Opioid Antagonists**

[00193] One novel method of deterring or minimizing cannabinoid agonist misuse, abuse and tampering is to target other co-abused drugs that are not part of the abuse deterrent dosage form but which are frequently found in the systemic circulation of drug abusers.

[00194] Forensic analytical toxicology studies have repeatedly revealed that in a majority of subjects, there are multiple drugs of abuse in the systemic circulation and importantly, such polydrug abuse is believed to be an important contributor to the death of many subjects from drug abuse and intentional or unintentional drug overdose. This observation of the use of multiple drugs of abuse in the same subject, i.e., polydrug abuse has also been reported in the drug abuse and addiction medicine literature, where positive urine samples ("dirty urine") frequently contains more than one illicit drug. For example, a majority of opioid-dependent individuals seeking treatment are polydrug abusers. The secondary illicit drug used most frequently in this population is marijuana. Prevalence estimates of marijuana use have ranged from 25% to 80% among cocaine and opioid abusers (Ball et al., 1988; Budney et al., 1996; Miller et al., 1990; Nirenberg et al., 1996; Saxon et al.,1993). Budney et al (Addiction, 1998) evaluated marijuana use among opioid abusers in patients enrolled in treatment for opioid dependence. Sixty-six per cent of participants were current marijuana users and almost all (94%) continued to use during treatment. In another study (Budney et al., Drug Abuse and Dependence, 1996) examining the relationship between marijuana

use and sociodemographic, psychosocial, and drug-use variables in treatment-seeking opioid abusers, marijuana involvement was associated with less stable relationships, more frequent alcohol use, more financial difficulty, and engagement in more risky behavior including intravenous drug use and needle-sharing.

[00195] The observation of polydrug abuse can be exploited to deter cannabinoid agonist abuse indirectly by antagonizing the pleasurable and mood altering effects of opioid agonists which are not part of the dosage form of the invention but may nevertheless co-abused by cannabinoid agonist abusers.

[00196] In certain embodiments, the present invention comprises a releasable cannabinoid agonist and a substantially releasable opioid antagonist, said oral dosage form not directed at deterring or reducing the abuse potential of the cannabinoid agonist contained therein by pharmacologic antagonism of cannabinoid agonist action by the opioid antagonist; said dosage form instead directed, and in some embodiments, solely directed at *indirectly* deterring abuse, misuse, diversion and tampering of the cannabinoid agonist by antagonizing the effects of co-abused opioid agonists which are not part of the dosage form of the invention but which are present in systemic circulation as co-abused drugs in the setting of polydrug abuse.

[00197] In certain embodiments, the present invention comprises a releasable cannabinoid agonist and a substantially releasable opioid antagonist; said oral dosage form directed at preventing the unapproved or surreptitious use of pharmaceutical grade or "street" grade opioid agonists for their mood altering effects by individuals who have been expressly informed by their clinicians not to take opioid agonists due to a risk of misuse, abuse, addiction, drug-drug interaction or due a contraindication to the opioid agonists; said substantially releasable opioid antagonist in some embodiments not enhancing the efficacy of the cannabinoid agonist of the dosage form by more than 0%, or by more than about 1%, or 2%, or 3%, or 4%, or 5%, or 8%, or 10%, or 15%, or 20%, or 30%; and said substantially releasable opioid antagonist in some

embodiments not diminishing the efficacy of the cannabinoid agonist of the dosage form by more than 0%, or by more than about 1%, or 2%, or 3%, or 4%, or 5%, or 8%, or 10%, or 15%, or 20%, or 30%.

[00198] The object of the invention in some embodiments is to partially or substantially nullify the mood altering effects of opioid agonists in individuals who are prescribed cannabinoid agonists of the present invention and who are using said opioid agonists without the approval or medical supervision of their physician. The object of the invention is achieved by combining a releasable cannabinoid agonist and a substantially releasable opioid antagonist in oral dosage forms.

[00199] The object of the invention in some embodiments is to reduce the potential for misuse and abuse of oral cannabinoid agonist dosage forms, both when said dosage form is used at usual doses orally in conjunction with the misuse or abuse of medically unauthorized or illicit opioid agonists, and when the dosage form is tampered with in an attempt to extract the cannabinoid agonist contained therein. This is achieved by exploiting the observation that cannabinoids are abused in the setting of polydrug abuse, frequently involving opioid agonists which are obtained via legitimate prescriptions, diversion from medical sources and illicit, non-medical sources.. In the setting of polydrug abuse, the dosage form of the invention provides a substantial disincentive to use the cannabinoid agonist dosage form in conjunction with the misuse or abuse of medically unauthorized or illicit opioid agonists or to extract the cannabinoid agonist of the dosage form, since the opioid antagonist contained in the same dosage form will nullify the effects of any co-abused opioid agonist, the latter not being part of the dosage form. Thus, abuse deterrence in some embodiments is obtained not by any direct action of the opioid antagonist on the cannabinoid agonist; instead, the inclusion of an opioid antagonist in the drug reservoir of the dosage form containing the cannabinoid agonist is a strategic intervention to exploit the patterns of drug abuse and co-abuse by nullifying or minimizing the effects of opioid agonist present in the systemic circulation of the polydrug abuser. Additionally, the oral dosage

form of the invention also reduces the toxicity observed from polydrug abuse both in the setting of intentional abuse and accidental abuse.

**Cannabinoid Agonists**

**[00200]** A number of assays are available to determine whether a drug is a cannabinoid agonist or cannabinoid antagonist, using in vivo and in vitro bioassay systems (Howlett et al., Mol Pharmacol, 1988).

**[00201]** Cannabinoid agonists are known or readily determined by individuals who practice the art. Preferably, the cannabinoid agonist useful for the present invention may be selected from the group consisting of inhibitors of cannabinoid agonist metabolism (e.g., without limitation, URB602, an inhibitor of monoacylglycerol lipase which catalyzes 2-arachidonoylglycerol hydrolysis) THC, nabilone, dronabinol, cannabidiol, 9-THC propyl analog, cannabidiol, cannabidiol propyl analog, cannabinol, cannabichromene, cannabichromene propyl analog, cannabigerol, cannabinoid terpenoids, cannabinoid flavonoids, endocannabinoids, anandamide, (R)-methanandamide,and 2-arachidonoylglycerol, THC-like ABC tricyclic cannabinoid analogues, exemplified by HU210 and desacetyllevonantradol; synthetic AC bicyclic and ACD tricyclic cannabinoid analogues, exemplified by CP55940, and CP55244 and aminoalkylindole compounds, exemplified by WIN55212-2, and their or their pharmaceutically acceptable salts, prodrugs, esters, analogs, derivatives, solvates, complexes, polymorphs, hydrates and metabolites, as racemates or an individual diastereoisomers or enantiomeric isomers thereof or mixtures thereof. (Little et al., *Pharmacol. Biochem. Behav, 1989;Howlett et al., Neuropharmacology, 1990;Johnson et al,* In: *Cannabinoids as Therapeutic Agents* (Mechoulam, R., ed.), CRC Press, 1986; Howlett et al., Mol Pharmacol, 1988; D'Ambra et al., J Med Chem, 1992; Pacheco et al., J Pharmacol Exp Ther, 1991; Compton et al, J Pharmacol Exp Ther, 1992; Howlett et al, Pharmacol Rev, 2002; Fowler. Fundam Clin Pharmacol. 2006;20:549-62; Karanian and Bahr, Curr Mol Med 2006;6:677-84; Singh and Budhiraja, Methods Find Exp Clin Pharmacol 2006;28:177-83;

Mackie and Stella, AAPS J 2006;8:E298-306; Pavlopoulos, Curr Pharm Des 2006;12(14):1751-69.).

[00202] In certain embodiments, the cannabinoid agonist useful for the present invention may be selected from the group consisting of dexanabinol (HU211), BAY 38-7271, Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone, THC (delta-9-tetrahydrocannabinol), nabilone, dronabinol, cannabidiol, cannabinol, cannabichromene, cannabigerol, cannabigerol, anandamide, (R)-methanandamide, 2-arachidonoylglycerol, HU210, desacetyllevonantradol, CP55940, CP55244, URB602, or WIN55212-2 and their or their pharmaceutically acceptable salts, prodrugs, esters, analogs, derivatives, solvates, complexes, polymorphs, hydrates and metabolites, as racemates or an individual diastereoisomers or enantiomeric isomers thereof or mixtures thereof.

[00203] In certain embodiments, the cannabinoid agonist useful for the present invention may be selected from the group consisting of 9-THC propyl analog, endocannabinoids, cannabinoid terpenoids, cannabinoid flavonoids, inhibitors of cannabinoid agonist metabolism, inhibitors of monoacylglycerol lipase, cannabidiol propyl analogues, cannabichromene propyl analogues, THC-like ABC tricyclic cannabinoid analogues, synthetic AC bicyclic cannabinoid analogues, synthetic ACD tricyclic cannabinoid analogues, aminoalkylindole compounds or analogs of 2-Arylimino-5,6-dihydro-4H-1,3-thiazines and their or their pharmaceutically acceptable salts, prodrugs, esters, analogs, derivatives, solvates, complexes, polymorphs, hydrates and metabolites, as racemates or an individual diastereoisomers or enantiomeric isomers thereof or mixtures thereof.

[00204] In certain embodiments, the amount of the cannabinoid agonist in the claimed cannabinoid composition may be from about 10 ng to about 1000 mg, even up to about 2000 mg. More preferably, the amount of the cannabinoid agonist is from about 10 ng to about 1200 mg, even more preferably from about 0.1 mg to about 1000 mg, and most preferably, from about 0.1 mg to about 700 mg.

[00205] In certain embodiments, the amount of the cannabinoid agonists in the claimed cannabinoid composition may be from about 10 ng to about 1000 mg. In some preferred embodiments, the cannabinoid agonist may be selected from compounds disclosed in U.S. Patent No. 7,217,732, 7,214,716, 7,169,942, 7,109,216, 7,091,216, 7,057,051, 6,995,184, 6,972,295, 6,943,266, 6,903,137, 6,864,291, 6,864,285, 6,525,087, 6,524,805, 6,509,367, 6,284,788, 5,948,777, 5,939,429, and 5,605,906, and in U.S. Patent Application No. 20070167514, 20070123505, 20070105914, 20070099947, 20070088058, 20070088025, 20070087390, 20070060638, 20070032517, 20070027144, 20060293299, 20060241165, 20060172019, 20060106071, 20060089356, 20060079557, 20060074086, 20050272763, 20050267161, 20050245554, 20050239828, 20050239133, 20050234061, 20050203112, 20050182103, 20050165118, 20050154202, 20050137173, 20050101542, 20050096379, 20050065189, 20050054679, 20050026986, 20050009902, 20040266861, 20040266841, 20040248956, 20040242593, 20040235854, 20040229928, 20040229850, 20040171613, 20040106614, 20040058820, 20040044051, 20040034090, 20040018151, 20030175822, 20030138508, 20030114495, 20020173528, 20020128302, 20020077322, and 20010034344, and their or their pharmaceutically acceptable salts, prodrugs, esters, analogs, derivatives, solvates, complexes, polymorphs, hydrates and metabolites, as racemates or an individual diastereoisomers or enantiomeric isomers thereof or mixtures thereof. All of the above patents and patent applications are hereby incorporated by reference in their entirety.

[00206] For purposes of the present invention, the term "cannabinoid agonist" shall include combinations of more than one cannabinoid agonist, and also include the unsalified agonist, mixed agonist-antagonists, partial agonists, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and mixtures thereof.

[00207] Some of the cannabinoid agonists and opioid antagonists disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present

invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

[00208] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms is space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[00209] The term "chiral center" refers to a carbon atom to which four different groups are attached.

[00210] The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

[00211] The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

[00212] The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

[00213] Notwithstanding the above definitions of "cannabinoid agonist", for the purposes of the present invention, 1) drugs that enhance the effect of cannabinoid agonists by inhibiting their metabolism or reuptake (for example, anandamide amidase inhibitors) are considered to be cannabinoid agonists; 2) drugs that induce anandamide amidase inhibitor metabolism or induce $CB_1$, $CB_2$ and non-$CB_1$/non-$CB_2$ cannabinoid agonist metabolism or enhance reuptake will be considered cannabinoid antagonists; 3) inverse cannabinoid agonists will be considered cannabinoid antagonists.

**Opioid Agonists/Antagonists**

[00214] The term "opioid receptor" includes mu (μ), delta (δ), kappa (κ) and/or nociceptin/orphanin FQ (N/OFQ) peptide (NOP) receptors, their subtypes and splice variants such as $\mu_1$, $\mu_2$, $\delta_1$, $\delta_2$, $\kappa_1$, $\kappa_2$ and $\kappa_3$, etc, regardless of whether they also bind to or influence other receptor systems (e.g., norepinephrine reuptake inhibition, serotonin reuptake inhibition, NMDA receptor antagonism).

[00215] For the purposes of this invention, the term "opioid" is interchangeable with the term "opioid agonist", except when there is a specific reference to an opioid antagonist.

[00216] Opioid agonists include alfentanil, allylprodine, alphaprodine, anileridine, apomorphine, apocodeine, benzylmorphine, bezitramide, brifentanil, buprenorphine, butorphanol, carfentanil, clonitazene, codeine, cyclorphen, cyprenorphine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxyaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydroxymethylmorphinan, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, methylmorphine, metopon, mirfentanil, morphine, morphine-6-glucuronide, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nociceptin/orphanin FQ (N/OFQ), normorphine, norpipanone, ohmefentanyl, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, pholcodine, piminodine, piritramide, propheptazine, promedol, profadol, properidine, propiram, propoxyphene, remifentanil, sufentanil, tapentadol, tramadol, trefentanil, tilidine, nalbuphine, or any opioid having agonist activity at an opioid receptor belonging to the phenanthrene, morphinan, benzomorphan, methadone, phenylpiperidine, propionanilide 4-anilidopiperidine, 4-aryl piperidines, and 4-Heteroarylpiperidines class, any opioid having agonist activity at an opioid receptor having the same

pentacyclic nucleus as nalmefene, naltrexone, buprenorphine, levorphanol, meptazinol, pentazocine and dezocine, any drug having agonist activity at an opioid receptor which is a fentanyl analog, or their pharmaceutically acceptable salts, prodrugs, esters, analogs, derivatives, solvates, complexes, polymorphs, hydrates and metabolites, as racemates or an individual diastereoisomers or enantiomeric isomers thereof or mixtures thereof. Opioid agonists also include drugs that bind to opioid receptors to exert agonist activity and are listed in the United States Controlled Substances Act of 1970, as amended, and regulations thereof, and drugs listed in the United States Psychotropic Substances Act of 1978, as amended, and regulations thereof.

[00217] The term "opioid antagonist" or "opioid receptor antagonist" means an antagonist substance that binds to one or more opioid receptor to exert an antagonist effect.

[00218] Opioid antagonists are known or readily determined by individuals who practice the art. Preferably, the opioid antagonists useful for the present invention may be selected from the group consisting of naltrexone, methylnaltrexone, nalbuphine, naloxone, nalmefene, cyclazocine, cyclorphan, oxilorphan nalorphine, nalorphine dinicotinate, nalmefene, nadide, levallorphan, N-methylnaltrexone, N-allyllevallorphan, N-methylnaltrexone, alvimopan, N-methylnalmefene and N-allyllevallorphan.

[00219] In some embodiments, the present invention includes a dosage form which comprises a releasable form of an opioid antagonist.

[00220] In some embodiments, the present invention relates to cannabinoid agonist in releasable form and *opioid* antagonist in substantially releasable form when administered intact, said dosage forms having reduced potential for abuse in cannabinoid agonist abusers and in polydrug abuse involving opioids. In some embodiments, the invention achieves its abuse deterrence by a novel method, namely by the effects of the opioid antagonist on co-used or co-abused opioid agonists under conditions where the dosage form of the invention used in the presence of opioid agonist, or in excess quantities by the

oral route intact, or upon administration by the non-oral route after tampering (e.g., solvent extraction, followed by inhalational, intranasal or parenteral use).

[00221] In certain embodiments, the opioid antagonist present in a substantially releasable form does not substantially block the therapeutic effects of the cannabinoid agonist when the dosage form is administered as intended, but wherein the effect of the cannabinoid agonist is at least partially blocked by the opioid antagonist when said dosage form is abused or tampered.

[00222] In certain embodiments, the amount of opioid antagonist in the claimed cannabinoid composition may be from about 10 ng to about 2000 mg, more preferably 10 ng to 1000 mg, and even more preferably 0.1 mg to 800 mg or 0.1 mg to 600 mg.

[00223] The amount of opioid antagonist required to produce the desired aversive effect or mood nullifying effect will vary, but can be determined based on the physicochemical, pharmaceutical properties and the pharmacology of the drug, including its oral bioavailability, half life, intrinsic clearance, potency, absolute bioavailability, potency, safety, its antagonism of opioid agonist and cannabinoid agonist effects and the like, and the magnitude of desired aversive effect.

[00224] The invention is also directed to methods of preventing abuse of a cannabinoid agonist utilizing the dosage forms disclosed herein. The method can comprise providing the cannabinoid agonist in releasable form in an oral dosage form together with an opioid antagonist in substantially releasable form.

[00225] Another embodiment of the invention is directed to a method of decreasing the abuse of a cannabinoid agonist or co-used or coabused opioid agonist in an oral dosage form, comprising preparing an oral dosage form as disclosed herein. For example, the method can comprise preparing a dosage form which comprises (i) an orally therapeutically effective amount of a cannabinoid agonist and (ii) an opioid antagonist in a substantially releasable form such that said dosage form provides a desired therapeutic effect and said antagonist does not substantially block the effect of the cannabinoid agonist

when said dosage form is administered orally intact. In alternative embodiments, the effect of the cannabinoid agonist is at least partially blocked when said dosage form is tampered with, e.g., dissolved in a solvent, and administered intranasally, by inhalation, parenterally or sublingually.

[00226] The invention is also directed to methods of preparing the dosage forms disclosed herein.

[00227] The oral dosage form containing a cannabinoid agonist in combination with a substantially releasable form of an opioid antagonist includes, but are not limited to tablets or capsules.

[00228] The dosage forms of the present invention may include any desired pharmaceutical excipients known to those skilled in the art. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in the Handbook of Pharmaceutical Excipients, APhA Publications; 5 edition (January 5, 2006), compounds found on the FDA EAFUS database (http://vm.cfsan.fda.gov/~dms/eafus.html); FDA Food Additives Status List (http://www.cfsan.fda.gov/~dms/opa-appa.html); FDAGRAS list and database; FDA Color Additive Status List (http://www.cfsan.fda.gov/~dms/opa-appc.html); FDA Inactive Ingredients Database (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm); Rowe, Sheskey and Owen, Handbook of Pharmaceutical Excipients, APhA Publications; 5th edition (2006); Remington: The Science and Practice of Pharmacy, 21st ed, Lippincott Williams & Wilkins (2005); United States Pharmacopeia–National Formulary (USP-NF), (USP 30 – NF 25, 2007), the International Programme on Chemical Safety (http://www.inchem.org/) and Health Canada's List of Acceptable Non-medicinal Ingredients (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/nmi-imn_list1_e.html), all hereby incorporated by reference in their entirety.

[00229] The benefits of the abuse-resistant dosage form are especially great in connection with oral dosage forms of potent cannabinoid agonists, which can provide valuable therapeutic benefits but are prone to being abused. This is

particularly true for sustained release cannabinoid agonist products which have a large dose of a desirable cannabinoid agonist intended to be released over a period of time in each dosage unit. Drug abusers take such sustained-release product and crush, grind, extract or otherwise damage the product so that the full contents of the dosage form become available for immediate absorption. Since such tampering of the dosage form of the invention results in the cannabinoid antagonist also becoming available for absorption, the present invention provides a means for deterring such abuse. In addition, the present invention addresses the risk of overdose to ordinary patients from "dumping" effect of the full dose of the cannabinoid agonist if the product is accidentally chewed or crushed.

[00230] The invention may provide for a safer product (e.g., lower risk of cannabinoid agonist toxicity or opioid agonist toxicity in the setting of polydrug abuse), if the product is misused, as well as one with less risk of abuse.

[00231] In certain embodiments, a combination of two cannabinoid agonists is included in the formulation with the opioid antagonist. In further embodiments, one or more cannabinoid agonist and an opioid antagonist is included and a further non-cannabinoid drug is also included for the treatment of the same medical condition as the cannabinoid agonist or for the treatment of a different medical condition. In certain embodiments, a combination of two or more opioid antagonists for interfering with the same or a different type of abuse (e.g., two cannabinoid antagonists; a cannabinoid antagonist and an opioid antagonist) are included in the dosage form.

[00232] In yet other embodiments, the dosage form is co-administered with a non-cannabinoid agonist for the treatment of the same medical condition as the cannabinoid agonist or for the treatment of a different medical condition. All modes of co-administration are contemplated, including via oral, subcutaneous, direct intravenous, slow intravenous infusion, continuous intravenous infusion, intravenous or epidural patient controlled analgesia (PCA and PCEA), intramuscular, intrathecal, epidural, intracisternal,

intramuscular, intraperitoneal, transdermal, topical, transmucosal, buccal, sublingual, transmucosal, inhalation, intranasal, epidural, intra-atricular, intranasal, rectal or ocular routes.

[00233] All oral pharmaceutical dosage forms of the invention are contemplated, including oral suspensions, tablets, capsules, caplets, lozenges, effervescent tablets, transmucosal films, buccal products, oral mucoretentive products, orally dissolving tablets, orally disintegrating tablets, and the like, administered as immediate release, sustained release, delayed release, modified release, controlled release, extended release and the like.

[00234] In certain embodiments, the dosage form may include, in addition to the releasable cannabinoid agonist and the substantially releasable cannabinoid antagonist, other abuse deterrent substances in releasable or substantially non-releasable form, including various aversive agents know to practitioners of the art.

[00235] Depending upon the particular route of administration, a variety of pharmaceutically-acceptable carriers, well known in the art may be used. Nonlimiting examples are sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, and pyrogen-free water.

[00236] In some embodiments, the cannabinoid agonist or opioid agonist and a non-cannabinoid included substance is a salt or complex of inorganic cation salts, organic salts such primary, secondary, tertiary and quaternary amines include substituted amines In some embodiments, examples of suitable pharmaceutically acceptable salts of xenobiotic include any of the inorganic cation salts such as sodium, potassium, lithium, magnesium, calcium, cesium, ammonia, ferrous, zinc, manganous, aluminum, ferric, and manganic; organic salts with primary, secondary, tertiary and quaternary amines, or mixtures thereof. Examples of such primary, secondary, tertiary and quaternary amines include substituted amines including but not limited to naturally occurring substituted amines, cyclic amines, basic ion exchange

resins, and mixtures thereof. More specifically, suitable amines include but are not limited to tromethamine, triethylamine, tripropylamine, dropopizine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, arginine, ornithine, histidine, caffeine, procaine, *N*-ethylpiperidine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, *tris*-(hydroxymethyl)aminomethane, N-methylglucamine, methylglycamine, theobromine, piperazine, piperidine, polyamine resins and the like, and mixtures thereof.

[00237] In some embodiments, examples of suitable pharmaceutically acceptable salts include aminoalcohols chosen from the group consisting of ethanolamine, 3-amino-1-propanol, (*R*)-1-amino-2-propanol, (*S*)-1-amino-2-propanol, 2-amino-1,3-propandiol, *N*-(2-hydroxyethyl)pyrrolidine, D-glucamine and L-prolinol, D-glucosamine, and *N*-methylglucosamine.

[00238] In some embodiments, examples of suitable pharmaceutically acceptable salts include alkali and alkaline earth metals and salts of an organic nature, such as the salts of basic amino acids.

**Additional Aversive Agent – Abuse Intervention Agents**

[00239] In certain preferred embodiments of the invention, the dosage form optionally comprises, in addition to the foregoing cannabinoid agonist and the opioid antagonist, one of more additional agents that are referred to herein as an abuse intervention agent(s), in sequestered, partially sequestered, unsequestered, non-releasable, partially releasable or releasable form. The abuse intervention agent(s) may comprise, for example, laxatives, cutaneous vasodilators, headache producing agents, emetics, emetogenic compound, nausea producing compounds, bittering agents, drugs that cause burning on irritation when in contact with tissue or mucous membranes (e.g., naso-mucosal irritants, oro-mucosal irritants, respiratory irritants), tissue irritants, gastrointestinal irritants, drugs that precipitate withdrawal effects, tissue dyes, lakes and colorants, beverage dyes, lakes and colorants, non-tissue staining beverage dyes, lakes and colorants (i.e, that do not stain or discolor the skin upon ingestion), fecal discolorants, urine discolorants, malodorous agents, opioid antagonists, benzodiazepine antagonists (e.g., flumazenil), and the like.

[00240] In certain particularly preferred embodiments of the invention, the abuse intervention agents are further selected from the group comprising (i) laxatives; (ii) cutaneous vasodilators; (iii) headache producing agents; (iv) emetics, emetogenic and nausea producing compounds; (iv) bittering agents (v) mucosal, naso-mucosal, oro-mucosal, respiratory, tissue and gastrointestinal irritants; (vi) tissue staining, non-tissue staining and beverage staining dyes, lakes and colorants; (vii) fecal and urine discolorants; and (viii) malodorous agents.

[00241] In certain particularly preferred embodiments of the invention, the abuse intervention agent comprises a non-toxic dye to deter surreptitious attempts at intoxication of another subject (e.g., in an alcoholic or non-alcoholic beverage).

[00242] In certain particularly preferred embodiments of the invention, the dosage form comprises an abuse intervention agent which comprises a non-toxic bittering agent to deter surreptitious attempts at intoxication of another subject (e.g., in an alcoholic or non-alcoholic beverage).

[00243] In certain particularly preferred embodiments of the invention, the dosage form comprises an abuse intervention agent which comprises a non-toxic bittering agent to deter oral or nasal ingestion of the dosage form.

[00244] In certain particularly preferred embodiments of the invention, the dosage form comprises an abuse intervention agent which comprises a non-toxic nasal irritant to deter oral or nasal ingestion of the dosage form.

[00245] In some embodiments, the abuse intervention agent(s) may be in the dosage form in an amount that does not produce an aversive effect or aversion in any, many or substantially all patients when taken in accordance with the prescribing information or the manufacturer's instructions (for example, in small quantities), but which produce an aversive effect when taken in excess (e.g., higher dose or more frequently).

[00246] In some embodiments, the abuse intervention agent is one or more bittering agents selected from the group comprising T2R or TAS2R receptor agonists, phenylthiourea (phenylthiocarbamide), natural, artificial and

synthetic flavor oils, flavoring aromatics, flavoring oils, oleoresins, spearmint oil, peppermint oil, eucalyptus oil, oil of nutmeg, allspice, mace, oil of bitter almonds, menthol, citrus oils including lemon, orange, lime, grapefruit, and fruit essences, sucrose derivatives, sucrose octaacetate, chlorosucrose derivatives, quinine, denatonium, denatonium saccharide and denatonium benzoate.

[00247] In some embodiments, the abuse intervention agent is one or more naso-mucosal, oro-mucosal, respiratory or tissue irritants selected from the group comprising transient receptor potential vanilloid 1 agonists, resiniferanoids, capsaicinoids, phorboid vanilloids, terpenoid 1,4-unsaturated dialdehydes, capsaicin, capsaicin analogs, resiniferatoxin, olvanil, piperine, zingerone, anandamide, 12- and 15-(S)-hydroperoxy-eicosatetraenoic acids, 5 ¬and 15-(S)-hydroxyeicosatetraenoic acids, phorbol 12-phenylacetate 13-acetate 20-homovanillate, 2 phorbol 12,13-didecanoate 20-homovanillate, leukotriene B(4), tinyatoxin, heptanoylisobutylamide, N-(3-acyloxy-2-benzylpropyl)-N'-dihydroxytetrahydrobenzazepine, tetrahydroisoquinoline thiourea analogs, heptanoyl guaiacylamide, isobutylamides, guaiacylamides, dihydrocapsaicin, homovanillyl octylester, nonanoyl vanillylamide, formic acid, acetic acid, propionic acidy, butyric acid, valeric acid, caproic acid, caprillic acid, capric acid, oxalic acid, malonic acid, succicnic acid, glu¬taric acid, adipic acid, maleic acid, fumaric acid, citric acid, sodium lauryl sulfate, poloxamer, sorbitan monoesters, glyceryl monooleates, niacin, mustard, allyl isothiocyaanate and p-hydroxybenzyl isothiocyanate and acetylsalicylic acid.

[00248] In some embodiments, the abuse intervention agent is one or more emetogenic or nausea producing agents selected from the group comprising zinc and pharmaceutically acceptable salts thereof, dopamine agonists, apomorphine, ipecac, ipecacuanha, emetine, methylcephaeline, cephaeline, psychotrine, O-methylpsychotrine, ammonium chloride, potassium chloride, magnesium sulfate, ferrous gluconate, ferrous sulfate, aloin, algarot or antimonious oxychloride, antimony trichloride, folate, folic acid, niacin and nicotinamide.

[00249] In some embodiments, the abuse intervention agent is one or more cutaneous vasodilators selected from the group comprising niacin, nicotinuric acid, beta-hydroxybutyrate and nicotinic receptor agonists, including agonists at nicotinic receptor HM74A and nicotinic receptor GPR109A.

[00250] In some embodiments, the abuse intervention agent is one or more tissue dyes, lakes or colorants, or beverage dyes, lakes or colorants, or a beverage dye, lake and colorant that does not stain or discolor the skin upon ingestion, or a fecal discolorant or a urine discolorant selected from the group comprising Curcumin, Riboflavin, Tartrazine, Quinoline yellow, Sunset yellow FCF, Carmine, Carmoisine, Amaranth, Ponceau 4R, Erythrosine, Allura red AC, Patent blue V, Indigo carmine, Brilliant blue FCF, Chlorophylls, Copper complexes of chlorophylls and chlorophyllins, Green S, Caramel, Brilliant black BN, Vegetable carbon, Carotenoids, Alpha-, beta-, gamma-carotene, Capsanthin, Capsorubin, Lycopene, Beta-apo-8′ carotenal, Ethyl ester of beta-apo-8′ carotenoic acid, Xanthophylls, Lutein, Canthaxanthin, Beetroot red, Anthocyanins, Cyanidin, Delphidin, Malvidin, Pelargonidin, Peonidin, Petunidin, Calcium carbonate, Titanium dioxide, Iron oxides and hydroxides, Aluminum, Brilliant blue FCF, Indigotine, Alphazurine FG, Indanthrene blue, Fast green FCF, Alizarin cyanine green F, Quinizarine green SS, Pyranine concentrated, Orange II, Dibromofluorescein, Diiodofluorescein, Erythrosine yellowish Na, Erythrosine, Ponceau SX, Lithol rubin B, Lithol rubin B Ca, Toney red, Tetrabromofluorescein, Eosine, Tetrachlorotetrabromofluorescein, Phloxine B, Helindone pink CN, Brilliant lake red R, Acid fuchsine, Lake bordeaux B, Flaming red, Alba red, Allura red AC, Allura Red AC, Alizurol purple SS, Tartrazine, Sunset yellow, FCF, Fluorescein, Naphthol yellow S, Uranine, Quinoline yellow WS, Quinoline yellow SS, Brilliant blue FCF, Indigotine, Alphazurine FG, Alizurol purple SS, Sunset yellow FCF, Alumina, Aluminum powder, Annatto extract, Beta-carotene, Bismuth oxychloride, Bronze powder, Calcium carbonate, Canthaxanthin, Caramel, Chromium-cobalt-aluminum oxide, Chromium hydroxide green, Chromium oxide green, Cochineal extract, carmine, Copper

powder, Dihydroxyacetone, Ferric ammonium citrate, Ferric ammonium ferrocyanide, Ferric ferrocyanide, Guanine, Iron oxides synthetic, Logwood extract, Mica, Potassium sodium copper chlorophyllin, Pyrogallol, Pyrophyllite, Talc, Titanium dioxide, Zinc oxide, FD&C blue #1, FD&C blue #2, D&C blue #4, D&C blue #9, FD&C green #3, D&C green #5, D&C green #6, D&C green #8, D&C orange #4, D&C orange #5, D&C orange #10, D&C orange #11, FD&C red #3, FD&C red #4, D&C red #6, D&C red #7, D&C red #17, D&C red #21, D&C red #22, D&C red #27, D&C red #28, D&C red #30, D&C red #31, D&C red #33, D&C red #34, D&C red #36, D&C red #39, FD&C red #40, FD&C red #40 lake, D&C violet #2, FD&C yellow #5, FD&C yellow #6, D&C yellow #7, Ext. D&C yellow #7, D&C yellow #8, D&C yellow #10, D&C yellow #11, FD&C lakes, D&C lakes, Ext. D&C lakes, FD&C blue #1 lake, FD&C blue #2 lake, D&C blue #4 lake, FD&C green #3 lake, D&C green #5 lake, D&C green #6 lake, D&C orange #4 lake, D&C orange #5 lake, D&C orange #10 lake, D&C orange #11 lake, FD&C red #4 lake, D&C red #6 lake, D&C red #7 lake, D&C red #17 lake, D&C red #21 lake, D&C red #22 lake, D&C red #27 lake, D&C red #28 lake, D&C red #30 lake, D&C red #31 lake, D&C red #33 lake, D&C red #34 lake, D&C red #36 lake, D&C violet #2 lake, FD&C yellow #5 lake, FD&C yellow #6 lake, D&C yellow #7 lake, Ext. D&C yellow #7 lake, D&C yellow #8 lake, D&C yellow #10 lake, Turmeric, Lactoflavin, Cochineal, carminic acid, Indigotine, Magnesium chlorophyll, Brilliant green BS, Black PN, Carbo medicinalis vegetabilis, Paprika oleoresin, Paprika oleoresin, Betanin, Beta-carotene, indigo carmine, iron oxides, sunset yellow FCF, titanium dioxide, E100, E101, E102, E104, E110, E120, E122, E123, E124, E127, E129, E131, E132, E133, E140, E141, E142, E150, E151, E153, E160, E161, E162, E163, E170, E171, E172, E173 and phenazopyridine.

[00251] In some embodiments, the abuse intervention agent is one or more laxatives selected from the group comprising Bis(p-hydroxyphenyl)pyridyl-2-methane, bisacodyl, bisoxatin, anthraquinone, anthraquinone analogs and derivatives (e.g., buckthorn, casanthranol, cascara, hydroxyanthracene,

glucofrangulin ), dantron, danthron, docusate (e.g., docusate sodium, docusate calcium, docusate potassium), gastrointestinal chloride channel activators (e.g., chloride channel subtype 2 activators), lubiprostone, magenesium salts (e.g., magnesium citrate, magnesium hydroxide, magnesium oxide), mannitol, oxyphenisatine, polyethylene glycol, poly(ethylene oxide) [PEO-1500], sodium phosphate, phenolphthalein, senna, senna constituents and derivatives (e.g., sennoside A, sennoside B) and sodium picosulfate.

[00252] In some embodiments, the abuse intervention agent may be added to the formulation in an amount of less than about 80% by weight, preferably less than about 60% by weight, more preferably less than about 40% by weight of the dosage form, even more preferably less than about 20% by weight of the dosage form, and most preferably less than about 10 by weight of the dosage form (e.g., 0.000000000000001% to 1%, or 0.000000001% to 3%, or 0.0001% to 10%, or 0.001% to 5%, or 1% to 10%, or 0.001% to 2%, or 1% or 10%, or 2% to 7%) depending on the particular agent used.

[00253] In some embodiments, the abuse intervention agent in the dosage form may be about 0.00000000001 mg to about 2000 mg, or about 0.0000001 mg to about 1500 mg, or about 0.000001 mg to about 1000 mg, or about 0.0001 mg to about 1000 mg, or about 0.001 mg to about 1000 mg, or about 0.01 mg to about 1000 mg, or about 0.1 mg to about 1500 mg, or 1 mg to about 800 mg, or about 1 mg to about 500 mg, or about 1 mg to about 300 mg, or about 1 mg to about 150 mg, or about 5 mg to about 400 mg, or about 5 mg to about 200 mg, or about 0.00000000001 mg to about 200 mg, or about 0.00000000001 mg to about 100 mg, or about 0.00000000001 mg to about 50 mg, or about 0.0000001 mg to about 200 mg, or about 0.0000001 mg to about 100 mg, or about 0.00001 mg to about 400 mg, or about 0.0001 mg to about 300 mg.

[00254] In some embodiments, the amount of the abuse intervention agent in the dosage form of the present invention can be a fixed ratio in relation to the amount of cannabinoid agonist in the dosage form. By appropriately selecting the quantity of the abuse intervention agent in the dosage form, aversive effects can be avoided under conditions of proper medical use (e.g.,

manufacturers prescribing directions). However, under some conditions of abuse, for example excessive intake of the dosage form of the invention, the quantity of agent consumed will exceed the "no effect" or "minimum effect" threshold, thereby producing one or more aversive effects, for example, e.g., nausea, emesis, diarrhea, laxation, cutaneous vasodilation, headache, bitter taste, naso-mucosal irritation, oro-mucosal irritation, reduction of the pleasurable, mood altering, rewarding, reinforcing, or other psychic and physiologic effects of the cannabinoid agonist or a co-abused drug.

[00255] In some embodiments, the "no effect" or "minimum effect" threshold amount of the abuse intervention agent can be exceeded when the dosage form of the invention is taken in excess of the manufacturer's recommendation by a factor of about 1.5, or about 2, or about 2.5, or about 3, or about 4, or about 5, or about 6, or about 7, or about 8, or about 10, or more than 10. In some embodiments, the production of an aversive effect can reduce or stop further abuse of the dosage form, thereby reducing the harm or toxicity of the drug in the subject who is tampering, misusing or abusing the dosage form, e.g., addicts, drug abusers and recreational drug users.

**Treatments and Additional Active Drugs**

[00256] The cannabinoid agonist of the invention may be used for the prevention or treatment of any diseases and disorders, including without limitation, (i) pain; (ii) infectious, immunologic, cardiovascular, pulmonary, gastrointestinal, hepatic, biliary, nutritional, metabolic, endocrine, hematologic, oncologic, musculoskeletal, rheumatic, neurologic, psychiatric, genitourinary, gynecologic, obstetric, pediatric, otolaryngogologic, ophthalmic, dermatologic, dental, oral, and genetic disorders, diseases and maladies and signs and symptoms thereof; (iii) depression, schizophrenia, influenza, common colds, anxiety, panic attacks, agoraphobia, ADHD, insomnia, sleep disorders, nasal congestion, headaches, migraine, urinary incontinence, constipation, allergies, cough, pneumonia, COPD, asthma, fluid retention, acid reflux, peptic ulcers, hypertension, cardiac arrhythmias,

hypercholesterolemia, CHF, fever, diarrhea, back pain, myofascial pain, osteoarthritis, neuropathic pain, cancer pain, acute pain, diabetes, muscle spasms, and rheumatoid arthritis, and signs and symptoms thereof; (iv) disorders, diseases and maladies, and signs and symptoms thereof referred to in Harrison's Principles of Internal Medicine, 16th Edition, 2004, Kasper DL, Braunwald W, Fauci A, Hauser S, Longo D, and Jameson JL (eds)].

[00257] In some preferred embodiments, the dosage form of the invention is used for the prevention or treatment of Alzheimer's disease, schizophrenia, depression, alcoholism, Parkinson's disease, stroke, premature labor, endotoxic shock, hepatic cirrhosis, atherosclerosis, cancer, glaucoma, emesis, pain, multiple sclerosis, amyotrophic lateral sclerosis, encephalitis, Huntington's disease, obesity, memory impairment, cognitive impairment, hypertension, cardiogenic shock, cerebral ischemia, myocardial infarction, neurotoxicity, febrile seizures and various intestinal disorders.

[00258] In some preferred embodiments, the dosage form of the invention may be give concurrently or contemporaneously with other therapeutic agents, said agents either part of the dosage form of the invention or given separately by the oral or non-oral route of administration and preferably selected from the group comprising decongestants, analgesics, analgesic adjuvants, antidepressants, antipsychotics, anxiolytics, hypnotics, sedatives, anti-ADHD drugs, psychostimulants, drugs to treat urinary incontinence, antihistamines, expectorants, antitussives, diuretics, anti-inflammatory agents, antipyretics, antirheumatics, antioxidants, laxatives, local anesthetics, proton pump inhibitors, motility modifying agents, vasodilators, inotropes, beta blockers, beta adrenergic agonists, drugs to treat asthma and COPD, antiinfectives, anti-migraine agents, antihypertensives, antianginal agents, gastric acid reducing agents, anti-ulcer agents, anticoagulants, lipid and cholesterol lowering drugs, anti-diabetic drugs, anti-epileptics, hormones, smooth muscle relaxants, skeletal muscle relaxants, bronchodilators, vitamins, trace minerals, amino acids, biological peptides and drugs to treat various infectious, immunologic disorders, cardiovascular, pulmonary, gastrointestinal, hepatic, biliary,

nutritional, metabolic, endocrine, hematologic, oncologic, musculoskeletal, neurologic, psychiatric, genitourinary, gynecologic, obstetric, pediatric, otolaryngogologic, ophthalmic, dermatologic, dental, oral, and genetic disorders and diseases. The drug being used in combination therapy with the present invention can be administered by any route, including parenterally, orally, topically, transdermally, sublingually, and the like.

[00259] The dosage form of the present invention may further include, in addition to a cannabinoid agonist and opioid antagonist, one or more drugs that may or may not act synergistically therewith. Thus, in certain embodiments, a combination of two cannabinoid agonists may be included in the dosage form, in addition to the opioid antagonist. For example, the dosage form may include two cannabinoid agonists having different pharmaceutical, physicochemical or pharmacologic properties, such as half-life, solubility, potency, and a combination of any of the foregoing. In yet further embodiments, one or more cannabinoid agonist is included and a further non-cannabinoid drug is also included, in addition to the opioid antagonist. In a further embodiment, a non-cannabinoid drug is also included for the treatment of the same medical condition as the cannabinoid agonist or for a different medical condition. In some embodiments, the cannabinoid agonist is intended to prevent or treat acute or chronic pain. An included non-cannabinoid drug in such a dosage form may be used to provide additive, complementary, or synergistic therapeutic effects, including NSAIDs, NO-NSAIDs, COX-2 selective inhibitors, acetaminophen, nitroparacetamol, nitric oxide donors, tramadol, beta adrenergic agonists, alpha-2 agonists, selective prostanoid receptor antagonists, cannabinoid agonists, opioid receptor agonists, NO-opioid receptor agonists, local anesthetics, purinergic P2 receptor antagonists, NMDA receptor antagonists, gabapentin, pregabalin, gabapentinoids, ligands of alpha(2)delta subunits of voltage-gated calcium channels, neuronal nicotinic receptor agonists, calcium channel antagonists, sodium channel blockers, superoxide dismutase mimetics, p38 MAP kinase inhibitors, TRPV1 agonists, dextromethorphan, dextrorphan, ketamine, glycine receptor

antagonists, antidepressants, corticosteroids, and antiepileptics, and any other drugs that can be shown by a person proficient in the art to prevent or treat pain.

[00260] The formulations of the invention may be used to treat painful conditions. As used herein, the term "pain" includes: (i) peripheral neuropathic pain, e.g., acute and chronic inflammatory demeyelinating polyradiculopathy, alcoholic polyneuropathy, chemotherapy-induced polyneuropathy, complex regional pain syndrome (CRPS) Type I and Type II, entrapment neuropathies (e.g., carpal tunnel syndrome), HIV sensory neuropathy, iatrogenic neuralgias (e.g., postthoracotomy pain, postmastectomy pain), idiopathic sensory neuropathy, painful diabetic neuropathy, phantom limb pain, postherpetic neuralgia, trigeminal neuralgia, radiculopathy (e.g., cervical thoracic, lumbosacral), sciatica, acute herpes zoster pain, temporomandibular joint disorder pain and postradiation plexopathy; and (ii) central neuropathic pain, e.g., compressive myelopathy from spinal stenosis, HIV myelopathy, multiple sclerosis pain, Parkinson's disease pain, postischemic myelopathy, post postradiation myelopathy, poststroke pain, posttraumatic spinal cord injury and syringomyelia; and (iii) cancer associated neuropathic pain, e.g., chemotherapy induced polyneuropathy, neuropathy secondary to tumor infiltration or nerve compression, phantom breast pain, postmastectomy pain, postradiation plexopathy and myelopathy; (iv) chronic pain, e.g., back pain, rheumatoid arthritis, osteoarthritis, inflammatory pain, non-inflammatory pain, myofascial pain, fibromyalgia, cancer pain, visceral pain, somatic pain, pelvic pain, musculoskeletal pain, post-traumatic pain, bone pain and idiopathic pain; (v) acute pain, e.g, acute postsurgical pain (including laparoscopic, laparatomy, gynecologic, urologic, cardiothoracic, arthroscopic, gastrointestinal, neurologic, orthopedic, oncologic, maxillofacial, ophthalmic, otolaryngologic, soft tissue, plastic, cosmetic, vascular and podiatric surgery, including abdominal surgery, abdominoplasty, adenoidectomy, amputation, angioplasty, appendectomy, arthrodesis, arthroplasty, arthroscopy, bilateral cingulotomy, biopsy, brain surgery, breast biopsy, cauterization, cesarean

section, cholecystectomy, circumcision, commissurotomy, cordotomy, corneal transplantation, cricothoracotomy, discectomy, diverticulectomy, episiotomy, endarterectomy, endoscopic thoracic sympathectomy, foreskin restoration, fistulotomy, frenectomy, frontalis lift, fundectomy, gastrectomy, grafting, heart transplantation, hemicorporectomy, hemorrhoidectomy, hepatectomy, hernia repair, hypnosurgery, hysterectomy, kidney transplantation, laminectomy, laparoscopy, laparotomy, laryngectomy, lithotripsy, lobotomy, lumpectomy, lung transplantation, mammectomy, mammoplasty, mastectomy, mastoidectomy, mentoplasty, myotomy, mryingotomy, nephrectomy, nissen fundoplication, oophorectomy, orchidectomy, parathyroidectomy, penectomy, phalloplasty, pneumotomy, pneumonectomy, prostatectomy, psychosurgery, radiosurgery, ritidoplasty, rotationplasty, sigmoidostomy, sphincterotomy, splenectomy, stapedectomy, thoracotomy, thrombectomy, thymectomy, thyroidectomy, tonsillectomy, tracheotomy, tracheostomy, tubal ligation, ulnar collateral ligament reconstruction, ureterosigmoidostomy, vaginectomy, vasectomy, vulvectomy; renal colic; incisional pain; inflammatory incisional pain; nociceptive incisional pain; acute neuropathic incisional pain following surgery), renal colic, trauma, acute back pain, burn pain, burn dressing change pain, migraine pain, tension headache pain, acute musculoskeletal pain, acute exacerbation or flare of chronic back pain, acute exacerbation or flare of osteoarthritis, acute exacerbation or flare of chronic pain, breakthrough chronic non-cancer pain, breakthrough cancer pain, acute exacerbation or flare of fibromylagia, acute exacerbation or flare of rheumatoid arthritis, acute exacerbation or flare of myofacsial pain, acute exacerbation or flare of chronic idiopathic pain, acute exacerbation or flare of neuropathic pain, procedure related pain (e.g., arthroscopy, laparoscopy, endoscopy, intubation, bone marrow biopsy, soft tissue biopsy, catheterization), and other self-limiting pain states.

[00261] Perceptible Pain Relief, Confirmed Perceptible Pain Relief and Meaningful Pain Relief are assessed and defined as follows: At the time of dosing with the study medication, a trained member of study staff starts two

stopwatches for each patient. The patient is instructed to stop the first stopwatch at the time of perceptible pain relief and the second stopwatch at the time when they first experience meaningful pain relief. The usual definitions of the perceptible and meaningful pain relief are as follows: Perceptible Pain Relief is when the patient begins to feel any pain relieving effect from the drug. The patient is typically instructed as follows: "I would like you to stop the first stopwatch when you first feel any pain relief whatsoever. This does not mean you feel completely better, although you might, but when you first feel any difference in the pain that you have had". Meaningful Pain Relief is when the patient feels their pain relief is meaningful to them. The patient is typically instructed as follows: "I would like you to stop the second stopwatch when you have meaningful pain relief. That is, when the relief from the pain is meaningful to you". Confirmed Perceptible Pain Relief is Perceptible Pain Relief in those patients who go on to also have Meaningful Pain Relief.

[00262] The "drug effects" questionnaire assesses the extent to which subjects currently felt a drug effect, on a scale of 1 to 5 (1 = "I feel no effect from it at all"; 2 = "I think I feel a mild effect, but I'm not sure"; 3 = "I feel an effect, but it is not real strong"; 4 = "I feel a strong effect"; 5 = "I feel a very strong effect"). This questionnaire can be used to examine the overall drug effects of abusable drugs given intact and upon tampering, preferably in drug abusers and recreational drug users without the medical condition for which the drug is effective.

[00263] The "drug liking" questionnaire assesses the extent to which subjects currently like the effects of the drug on a 100-mm VAS, bounded on the left by "0 = dislike a lot", bounded on the right by "100 = like a lot". This questionnaire can be used to examine the overall drug liking of abusable drugs given intact and upon tampering, preferably in drug abusers and recreational drug users without the medical condition for which the drug is effective.

[00264] The "take again" questionnaire assesses whether subjects would take the abusable drug again if given the opportunity. The patient is asked "If given an opportunity, would you take this drug again? (circle one: YES or

NO). This questionnaire can be used to examine the overall desirability of the drug experience with the abusable drugs taken intact and taken after tampering, preferably in drug abusers and recreational drug users without the medical condition for which the drug is effective.

[00265] On the "coasting" questionnaire the patient is asked to put a mark on a horizontal line that best describes their response to the question: "Do you feel like you are coasting or spaced out? The horizontal line is a visual analog scale (VAS) bounded on the left by "not at all" and on the right by "extremely". This questionnaire can be used to examine the degree to which subjects feel like they are coasting or spaced out with the abusable drugs taken intact and taken after tampering, preferably in drug abusers and recreational drug users without the medical condition for which the drug is effective.

[00266] Three performance tasks may be employed for measuring skills related to driving.

[00267] The "critical tracking task" measures the patient's ability to control a displayed error signal in a first-order compensatory tracking task. The error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements correct the error by returning the cursor to the midpoint. The frequency at which the patient loses the control is the critical frequency. The critical tracking task measures the psychomotor control during a closed loop operation. It is a laboratory analog to on-the-road tracking performance.

[00268] The "stop signal task" measures motor impulsivity, which is defined as the inability to inhibit an activated or pre-cued response leading to errors of commission. The task requires patients to make quick key responses to visual go signals, i.e. the letters ABCD presented one at a time in the middle of the screen, and to inhibit any response when a visual stop signal, i.e. "*" in one of the four corners of the screen, is presented at predefined delays. The main dependent variable is the stop reaction time on stop signal trials that represents the estimated mean time required to inhibit a response.

[00269] The Tower of London (TOL) is a decision-making task that measures executive function and planning. The task consists of computer generated images of begin- and end-arrangements of three colored balls on three sticks. The subject's task is to determine as quickly as possible, whether the end-arrangement can be accomplished by "moving" the balls in two to five steps from the beginning arrangement by pushing the corresponding number coded button. The total number of correct decisions is the main performance measure.

[00270] For the purposes of in vivo testing, unless specified otherwise, pain intensity is measured on a VAS or categorical scale. On the categorical scale, the patient is asked "My pain at this time is: None = 0, Mild = 1, Moderate = 2, Severe = 3. On the VAS, the patient is asked "My pain at this time is" (with VAS anchors: "No Pain" and "Extreme Pain").

[00271] For the purposes of in vivo testing, unless specified otherwise, pain relief is measured on a categorical scale. The patient is asked "My relief from starting pain is: None = 0, A little = 1, Some = 2, A lot = 3, Complete = 4.

[00272] In certain preferred embodiments of the invention, wherein the cannabinoid agonist is an analgesic, the mean ratio of the time to confirmed perceptible pain relief after administration of the tampered dosage form to the time to confirmed perceptible pain relief after administration of the intact dosage form is more than 20:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 15:1, or more than about 10:1, or more than about 7:1, or more than about 5:1, or more than about 3:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than 1.15:1.

[00273] In certain preferred embodiments of the invention, wherein the cannabinoid agonist is an analgesic, the mean ratio of the time to meaningful pain relief after administration of the tampered dosage form to the time to meaningful pain relief after administration of the intact dosage form is more than 20:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 15:1, or more than about 10:1,

or more than about 7:1, or more than about 5:1, or more than about 3:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than 1.15:1.

[00274] In certain preferred embodiments of the invention, wherein the cannabinoid agonist is an analgesic, the mean ratio of the peak pain intensity difference score after administration of the intact dosage form to the peak pain intensity difference score after administration of the tampered dosage form is more than 10:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 8:1, or more than about 7:1, or more than about 5:1, or more than about 3:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1.

[00275] In certain preferred embodiments of the invention, wherein the cannabinoid agonist is an analgesic, the mean ratio of the peak pain relief score after administration of the intact dosage form to the peak pain relief score after administration of the tampered dosage form is more than 10:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 8:1, or more than about 7:1, or more than about 5:1, or more than about 3:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1.

[00276] In certain preferred embodiments of the invention, wherein the cannabinoid agonist is an analgesic, the mean ratio of change from baseline to two hours post-dose or four hours post-dose in pain intensity score after administration of the intact dosage form to the change from baseline to two hours post-dose in pain intensity score after administration of the tampered dosage form is more than 10:1; said pain score measured in acute postsurgical pan. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 9:1, or more than about 8:1, or more than about 7:1, or more than about 5:1, or more than about 3:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1.

[00277] In certain preferred embodiments of the invention, wherein the cannabinoid agonist is an analgesic, the mean ratio of the number of patients with pain who obtain 33% pain relief after administration of the intact dosage form when compared with following administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1.

[00278] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of the incidence and nausea intensity score in healthy subjects (previously naïve to cannabinoid agonist) after administration of the intact dosage form when compared with following administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1.

[00279] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of moderate or severe sedation or drowsiness in healthy subjects (naïve to cannabinoid agonist) after administration of the intact dosage form when compared with following administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1. Preferably, the aforementioned sedation is measured at 0.5, 1, 1.5, 2, 3, 4, 5 or 6 hours, or up to 1, 2, 3, 4, or 6 hours post-dose.

[00280] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of moderate or severe sedation or drowsiness in healthy subjects (naïve to

cannabinoid agonist) after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1; said dosage form administration followed about 0.5 hour later by alcohol (ethanol) administration sufficient to maintain a blood alcohol concentration of 0.04% to 0.08%.

[00281] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of the drug liking score in drug abusers and recreational drug users after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1. Preferably, the aforementioned drug liking score is measured at 1, 1.5, 2, 3, 4, 5 or 6 hours, or up to 1, 2, 3, 4, or 6 hours post-dose.

[00282] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of the score on the "take again" questionnaire in drug abusers and recreational drug users after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1. Preferably, the aforementioned take again score is measured at 1, 1.5, 2, 3, 4, 5 or 6 hours, or up to 1, 2, 3, 4, or 6 hours post-dose.

[00283] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of the score on the "coasting" questionnaire in drug abusers and recreational drug users after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1. Preferably, the aforementioned coasting score is measured at 2, 3, 4, 5 or 6 hours, or up to 2, 3, 4, or 6 hours post-dose.

[00284] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of impairment on the "critical tracking task" driving skills test in cannabinoid agonist naïve healthy subjects after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1. Preferably, the aforementioned critical tracking task score is measured at 1, 1.5, 2, 3, 4, 5 or 6 hours, or up to 1, 2, 3, 4, or 6 hours post-dose.

[00285] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of impairment on the "critical tracking task" driving skills test in cannabinoid agonist naïve healthy subjects after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1;

said "critical tracking task" driving skills test score measured 2.5 to 6 hours after administration of the dosage form, said dosage form administration followed about 1 hours later by alcohol (ethanol) administration sufficient to maintain a blood alcohol concentration of 0.04% to 0.08%.

[00286] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of impairment on the "stop signal task" driving skills test in cannabinoid agonist naïve healthy subjects after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1. Preferably, the aforementioned stop signal task score is measured at 1, 1.5, 2, 3, 4, 5 or 6 hours, or up to 1, 2, 3, 4, or 6 hours post-dose.

[00287] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of impairment on the "stop signal task" driving skills test in cannabinoid agonist naïve healthy subjects after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1; said "critical tracking task" driving skills test score measured 2.5 to 6 hours after administration of the dosage form, said dosage form administration followed about 1 hours later by alcohol (ethanol) administration sufficient to maintain a blood alcohol concentration of 0.04% to 0.08%.

[00288] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of impairment on the "Tower of London" driving skills test score in cannabinoid

agonist naïve healthy subjects after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1; or more than about 1:1. Preferably, the aforementioned Tower of London score is measured at 1, 1.5, 2, 3, 4, 5 or 6 hours, or up to 1, 2, 3, 4, or 6 hours post-dose.

[00289] In certain preferred embodiments of the invention, wherein the dosage form is given in conjunction with an opioid agonist, the mean ratio of impairment on the "Tower of London" driving skills test score in cannabinoid agonist naïve healthy subjects after administration of the intact dosage form when compared with administration of the tampered dosage form is more than 5:1. In other embodiments of the invention, the mean ratio using the aforementioned test method is more than about 4:1, or more than about 3:1, or more than about 2.5:1, or more than about 2:1, or more than about 1.5:1, or more than about 1.25:1, or more than about 1.15:1, or more than about 1:1; said "critical tracking task" driving skills test score measured 2.5 to 6 hours after administration of the dosage form, said dosage form administration followed about 1 hours later by alcohol (ethanol) administration sufficient to maintain a blood alcohol concentration of 0.04% to 0.08%.

[00290] In some embodiments, the dosage form of the invention is intended to prevent or treat Alzheimer's disease, schizophrenia, depression, alcoholism, Parkinson's disease, stroke, premature labor, endotoxic shock, hepatic cirrhosis, atherosclerosis, cancer, glaucoma, emesis, pain, multiple sclerosis, amyotrophic lateral sclerosis, encephalitis, Huntington's disease, obesity, memory impairment, cognitive impairment, hypertension, cardiogenic shock, cerebral ischemia, myocardial infarction, neurotoxicity, febrile seizures and various intestinal disorders. An included non-cannabinoid drug in such a dosage form may be used to provide additive, complementary, or synergistic therapeutic effects. Alternatively, the non-cannabinoid drug may be included

for the treatment a different medical condition. In certain preferred embodiments of the present invention, the invention allows for the use of lower doses of the cannabinoid agonist by virtue of the inclusion of an additional non-cannabinoid drug for the prevention or treatment of the same medical condition. By using lower amounts of either or both drugs, the side effects associated with treatment in humans are reduced.

**Preparation of Releasable Cannabinoid Agonist and Releasable or Substantially Releasable Opioid Antagonists as an Immediate Release Oral Dosage Form**

[00291] Pharmaceutical composition and methods of the present invention comprise one or more cannabinoid agonists in releasable form and one or more opioid antagonists releasable or substantially releasable.

[00292] In certain preferred embodiments of the invention, the dosage form optionally comprises, in addition to the foregoing, one of more abuse intervention agents in sequestered, partially sequestered, unsequestered, non-releasable, partially releasable or releasable form in unsalified form xenobiotics base or pharmaceutically acceptable salts in racemic or enantiomeric form, or mixtures thereof in and they are intended for oral administration.

[00293] All oral pharmaceutical dosage forms of the invention are contemplated, including oral suspensions, tablets, capsules, lozenges, effervescent tablets, effervescent powders, powders, solutions, powders for reconstitution, transmucosal films, buccal products, oral mucoretentive products, oral gastroretentive tablets and capsules, orally disintegrating tablets, fast dissolving tablets, fast dispersing tablets, fast disintegrating dosage forms, administered as immediate release, modified release, enteric coated, sustained release, controlled release, pulsatile release, delayed release, colonic delivery, targeted delivery and extended release dosage form.

[00294] The preparation of oral immediate release dosage forms is well known in the art - see Remington: the science of Pharmacy Practice, 21st Edition, 2006, Lippincott, Williams & Wilkins, Baltimore, MD; Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug

Selection to Commercial Dosage Form. Gibson, M (ed). CRC Press, 2001; Niazi, S. Handbook of Pharmaceutical Manufacturing Formulations: Uncompressed Solid Products (Volume 2 of 6), CRC Press, 2004; Niazi, S. Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products (Volume 1 of 6), CRC Press, 2004; Mollet, H, Grubenmann A, Payne H. Formulation Technology: Emulsions, Suspensions, Solid Forms, Wiley-VCH, 2001; Niazi S and Niazi SK (all of which are hereby incorporated by reference). A majority of oral dosage forms commercially available world wide are formulated as immediate release products. A wide variety of immediate release dosage forms can be formulated, including oral suspensions, tablets, capsules, lozenges, effervescent tablets, effervescent powders, powders, solutions, powders for reconstitution.

**Preparation of Controlled Release Dosage Forms Containing a Releasable Cannabinoid Agonist and a Releasable or Substantially Releasable Form of an Opioid Antagonist**

[00295] A combination of the cannabinoid agonist and a releasable or substantially releasable form of an opioid antagonist may be formulated as a controlled or sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may optionally include a sustained release carrier which is incorporated into a matrix along with the cannabinoid agonist and the opioid antagonist, or may be applied as a sustained release coating.

[00296] In one preferred embodiment of the present invention, the sustained release dosage form comprises such particles comprising the cannabinoid agonist and opioid antagonist, wherein the particles have diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm.

[00297] The cannabinoid agonist and opioid antagonist particles are preferably film coated with a material that permits release of the cannabinoid agonist and opioid antagonist at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, a desired in-vitro release rate. The sustained release coating formulations of the

present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic and inert.

[00298] The dosage forms comprising a cannabinoid agonist and opioid antagonist may optionally be coated with one or more materials suitable for the modulation of the cannabinoid agonist and/or opioid antagonist release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the cannabinoid agonist or opioid antagonist in desired areas of the gastro-intestinal (GI) tract, e.g., the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about six hours and preferably about twelve hours to up to about twenty-four hours of therapeutic effect to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release of the cannabinoid agonist and opioid antagonist regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

[00299] Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

[00300] In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the cannabinoid agonist and/or opioid antagonist is

coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile.

[00301] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate by weight of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 47.5% at 1 hour, from about 10% to about 65% at 2 hours, from about 15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours. In other preferred embodiments, the dosage form provides said an in-vitro release rate of from 0% to about 40% at 1 hour, from about 5% to about 55% at 2 hours, from about 10% to about 60% at 4 hours, from about 15% to about 70% at 6 hours, from about 25% to about 80% at 9 hours, and greater than about 50% at 12 hours.

[00302] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate by weight of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 47.5% at 1 hour, from about 10% to about 65% at 2 hours, from about

15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours.

[00303] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate by weight of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 47.5% at 1 hour, from about 10% to about 65% at 2 hours, from about 15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours; said in-vitro release rate being substantially independent of pH in that a difference, at any given time, between an amount of cannabinoid agonist released at one pH and an amount released at any other pH, when measured in-vitro using the USP Basket or Paddle Method of USP Drug Release test of U.S. Pharmacopeia (2003) at 100 rpm in 900 ml aqueous buffer, is no greater than 30%.

[00304] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for once-a-day administration to a human patient; said dosage form providing an in-vitro release rate by weight of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 30% at 1 hour, from about 10% to about 65% at 4 hours, from about 20% to about 70% at 8 hours, from about 25% to about 80% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours.

[00305] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for once-a-day administration to a human patient; said dosage form providing an in-vitro release rate by weight of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 30% at 1 hour, from about 10% to about 65% at 4 hours, from about 20% to about 70% at 8 hours, from about 25% to about 80% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours; said in-vitro release rate being substantially independent of pH in that a difference, at any given time, between an amount of cannabinoid agonist released at one pH and an amount released at any other pH, when measured in-vitro using the USP Basket or Paddle Method of USP Drug Release test of U.S. Pharmacopeia (2003) at 100 rpm in 900 ml aqueous buffer, is no greater than 30%.

[00306] In some preferred embodiments, the cannabinoid agonist dosage forms provide an in-vitro release of from 2% to about 50% by weight of the cannabinoid agonist or a pharmaceutically acceptable salt thereof from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 700 ml of Simulated Gastric Fluid (SGF) at 37 °C.

[00307] In some preferred embodiments, the cannabinoid agonist dosage form provides an in-vitro release from about 5% to about 45% by weight of the cannabinoid agonist or a pharmaceutically acceptable salt thereof from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 700 ml of Simulated Gastric Fluid (SGF) at 37 °C.

[00308] In some preferred embodiments, the cannabinoid agonist dosage form provides a $C_{max}$ of cannabinoid agonist which is less than 65% of the $C_{max}$ of an equivalent dose of an oral immediate release cannabinoid agonist solution.

[00309] In some preferred embodiments, the dosage form provides a time to 75% mean $C_{max}$ of cannabinoid agonist which is about 100% to about 2000% of the time to 75% mean $C_{max}$ of an oral immediate release cannabinoid agonist solution.

[00310] In some preferred embodiments, the dosage from maintains a plasma cannabinoid agonist concentration within 50% of $C_{max}$ for about 1 to about 9 hours during the 12 hour dosing interval.

[00311] In some preferred embodiments, the dosage from maintains a plasma cannabinoid agonist concentration within 50% of $C_{max}$ for about 1 to about 9 hours during the 24 hour dosing interval.

[00312] In some preferred embodiments, the dosage form provides a $T_{max}$ of cannabinoid agonist at a time point 1.5 to 20 times later than the $T_{max}$ provided by an equivalent dose of an immediate release cannabinoid agonist solution. In the dosage form provides a $T_{max}$ at a time point about 1.5 to 15 times late, or about of 1.5 to 10 times later, or about of 1.5 to 7 times later, or about of 1.5 to 3 times later, or about of 2 to 20 times later, or about of 2 to 10 times later, or about of 2 to 5 times later, or about of 2 to 3 times later, or about of 2.5 to 20 times later, or about of 2.5 to 8 times later, or about of 2.5 to 5 times later, or about of 2.5 to 4 times later, or about of 3 to 20 times later, or about of 3 to 10 times later, or about of 3 to 5 times later.

[00313] In some preferred embodiments, the dosage form provides a mean in vivo extent of absorption of cannabinoid agonist from 0 to 4 hours which is at least 20% of the mean in vivo extent of absorption from to 0 to 12 hours, wherein the mean in vivo extent of absorption is the area under the plasma or serum cannabinoid agonist concentration time curve from the time of drug administration to the specified time point. In other embodiments, said in vivo extent of absorption from 0 to 4 hours is at least about 5%, or at least about 10%, or at least about 15%, or at least about 25%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, at least about 90%, or about 100% of the mean in vivo extent of absorption from to 0 to 12 hours.

[00314] In some preferred embodiments, the dosage form provides a mean in vivo extent of absorption of cannabinoid agonist from 0 to 8 hours which is at least 20% of the mean in vivo extent of absorption from to 0 to 24 hours, wherein the mean in vivo extent of absorption is the area under the plasma or serum cannabinoid agonist concentration time curve from the time of drug administration to the specified time point. In other embodiments, said in vivo extent of absorption from 0 to 8 hours is at least about 5%, or at least about 10%, or at least about 15%, or at least about 25%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, at least about 90%, or about 100% of the mean in vivo extent of absorption from to 0 to 24 hours.

[00315] In some preferred embodiments, the dosage form provides a mean in vivo extent of absorption of cannabinoid agonist from 0 to 12 hours which is at least 20% of the mean in vivo extent of absorption from to 0 to 24 hours, wherein the mean in vivo extent of absorption is the area under the plasma or serum cannabinoid agonist concentration time curve from the time of drug administration to the specified time point. In other embodiments, said in vivo extent of absorption from 0 to 12 hours is at least about 5%, or at least about 10%, or at least about 15%, or at least about 25%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, at least about 90%, or about 100% of the mean in vivo extent of absorption from to 0 to 24 hours.

[00316] In some preferred embodiments, the dosage form provides a mean in vivo extent of absorption of cannabinoid agonist over the dosing interval (e.g., from 0 to 12 hours or from 0 to 24 hours) which is at least 40% of the mean in vivo extent of absorption from to 0 to $\infty$, wherein the mean in vivo extent of absorption is the area under the plasma or serum cannabinoid agonist concentration time curve (AUC) from the time of drug administration to the specified time point and where AUC infinity is the sum of AUC from time "0" to time "t" (the last quantifiable time point which has been sampled) plus the extrapolated AUC from the last quantifiable sampling time point to infinity.

[00317] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition of cannabinoid agonist or a pharmaceutically acceptable salt thereof or mixtures thereof, said dosage form providing an in-vitro release of between 0% to about 50% by weight of the cannabinoid agonist or a pharmaceutically acceptable salt thereof from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 700 ml of Simulated Gastric Fluid (SGF) at 37 °C.

[00318] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition of cannabinoid agonist or a pharmaceutically acceptable salt thereof or mixtures thereof, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% to about 80% at 0.5 hours, and greater than about 40% at 1 hour; or between 0% to about 90% at 0.5 hours, and greater than about 60% at 1 hour; or between 1.6 and 7.2 at 37 °C of between 0% to about 100% at 0.5 hours, and greater than about 60% at 1 hour.

[00319] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition of cannabinoid agonist or a pharmaceutically acceptable salt thereof or mixtures thereof, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% to about 90% at 1 hour, and greater than about 40% at 2 hours; or between 1.6 and 7.2 at 37 °C of between 0% to about 90% at 1 hour, and greater than about 70% at 2 hours; or between 1.6 and 7.2 at 37 °C of between 0% to about 50% at 1 hour, and greater than about 30% at 2 hours; between 1.6 and 7.2 at 37 °C of between 0% to about 30% at 1 hour, and greater than about 25% at 2 hours; or between 1.6 and 7.2 at 37 °C of between 0% to about 100% at 1 hour, and greater than about 60% at 2 hours.

[00320] In some preferred embodiments, the invention comprises an oral pharmaceutical dosage form providing an in-vitro release of between 0% to

about 50% by weight of the cannabinoid agonist or a pharmaceutically acceptable salt thereof from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 700 ml of Simulated Gastric Fluid (SGF) at 37 °C.

[00321] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 3% and about 95% at 4 hours and between about 10% and about 100% at 8 hours; or between 10% and about 65% at 1 hour, between about 20% and about 75% at 2 hours, between about 30% and about 95% at 4 hours and between about 40% and about 100% at 8 hours.

[00322] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% to about 47.5% at 1 hour, from about 10% to about 65% at 2 hours, from about 15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours.

[00323] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially

releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours; or between 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours; or between 0% to about 30% at 1 hour, from about 10% to about 65% at 4 hours, from about 20% to about 70% at 8 hours, from about 25% to about 80% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours; or between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 25% and about 100% at 12 hours, between about 30% and about 100% at 16 hours, between about 50% and about 100% at 24 hours, and greater than about 80% at 36 hours.

**[00324]** In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 20% and about 50% at 1 hour, between about 40% and about 75% at 2 hours, between about 60%

and about 95% at 4 hours, between about 80% and about 100% at 8 hours and between about 90% and about 100% at 12 hours.

[00325] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 10% and about 95% at 4 hours, between about 35% and about 100% at 8 hours, between about 55% and about 100% at 12 hours, between about 70% to about 100% at 16 hours, and greater than about 90% at 24 hours.

[00326] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% and about 30% at 1 hour, between about 0% and about 45% at 2 hours, between about 3% and about 55% at 4 hours, between about 10% and about 65% at 8 hours, between about 20% and about 75% at 12 hours, between about 30% to about 88% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours.

[00327] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said

dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 20% and about 100% at 12 hours, between about 30% to about 100% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours.

[00328] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 15% and about 25% at 1 hour, between about 25% and about 35% at 2 hours, between about 30% and about 45% at 4 hours, between about 40% and about 60% at 8 hours, between about 55% and about 70% at 12 hours and between about 60% to about 75% at 16 hours.

[00329] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of a cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, a releasable or substantially releasable opioid antagonist, and controlled release material to render said dosage form suitable for twice-a-day administration to a human patient; said dosage form providing an in-vitro release rate of cannabinoid agonist which is substantially independent of pH in that a difference, at any given time, between an amount of cannabinoid agonist released at one pH and an amount released at any other pH, when measured in-vitro using the USP Basket or

Paddle Method of USP Drug Release test of U.S. Pharmacopeia (2003) at 100 rpm in 900 ml aqueous buffer, is no greater than 30%.

[00330] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 700 ml of Simulated Gastric Fluid (SGF) at 37 °C of between 0% to about 50% by weight of the cannabinoid agonist. In other preferred embodiments, said release rate is between 0% to about 1%, or 0% to about 3%, or 0% to about 5%, or 0% to about 10%, or 0% to about 15%, or 0% to about 20%, 0% to about 30%, or 0% to about 40%, or 0% to about 60%, or 0% to about 70%, or 0% to about 80%, or 0% to about 90%, 0% to about 100%.

[00331] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 3% and about 95% at 4 hours and between about 10% and about 100% at 8 hours. In other preferred embodiments, said release rate is between 0% and about 10% at 1 hour, between about 0% and about 20% at 2 hours, between about 2% and about 80% at 4 hours and between about 5% and about 100% at 8 hours; or between 0% and about 20% at 1 hour, between about 0% and about 40% at 2 hours, between about 0% and about 80% at 4 hours and between about 2% and about 100% at 8 hours; or between 0% and about 40% at 1 hour, between about 0% and about 60% at 2 hours, between about 5% and about 85% at 4 hours and between about 5% and about 90% at 8 hours and greater than 20% at 12 hours;

or between 0% and about 50% at 1 hour, between about 0% and about 50% at 2 hours, between about 10% and about 90% at 4 hours and between about 15% and about 90% at 8 hours and greater than 30% at 12 hours; or between 0% and about 70% at 1 hour, between about 0% and about 70% at 2 hours, between about 10% and about 75% at 4 hours and between about 15% and about 90% at 8 hours and greater than 30% at 12 hours.

[00332] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 10% and about 65% at 1 hour, between about 20% and about 75% at 2 hours, between about 30% and about 95% at 4 hours and between about 40% and about 100% at 8 hours. In other preferred embodiments, said release rate is between 2% and about 70% at 1 hour, between about 5% and about 80% at 2 hours, between about 10% and about 90% at 4 hours and between about 20% and about 100% at 8 hours; or between 5% and about 60% at 1 hour, between about 10% and about 75% at 2 hours, between about 15% and about 85% at 4 hours and between about 30% and about 100% at 8 hours; or between 20% and about 70% at 1 hour, between about 20% and about 75% at 2 hours, between about 20% and about 90% at 4 hours and between about 40% and about 100% at 8 hours; or between 30% and about 80% at 1 hour, between about 40% and about 85% at 2 hours, between about 40% and about 90% at 4 hours and between about 60% and about 100% at 8 hours; or between 1% and about 20% at 1 hour, between about 5% and about 20% at 2 hours, between about 10% and about 40% at 4 hours and between about 20% and about 40% at 8 hours and greater than 40% at 12 hours.

[00333] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of

cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release rate by weight of the cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% to about 47.5% at 1 hour, from about 10% to about 65% at 2 hours, from about 15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours. In other preferred embodiments, said release rate is between 0% to about 30% at 1 hour, from about 5% to about 45% at 2 hours, from about 10% to about 60% at 4 hours, from about 15% to about 70% at 6 hours, from about 25% to about 80% at 9 hours, and greater than about 50% at 12 hours; or between 0% to about 20% at 1 hour, from about 2% to about 35% at 2 hours, from about 5% to about 50% at 4 hours, from about 10% to about 60% at 6 hours, from about 15% to about 70% at 9 hours, and greater than about 40% at 12 hours; or between 0% to about 10% at 1 hour, from about 1% to about 30% at 2 hours, from about 5% to about 40% at 4 hours, from about 10% to about 60% at 6 hours, from about 15% to about 70% at 9 hours, and greater than about 40% at 12 hours; or between 0% to about 5% at 1 hour, from about 0% to about 10% at 2 hours, from about 2% to about 20% at 4 hours, from about 5% to about 30% at 6 hours, from about 10% to about 40% at 9 hours, and greater than about 30% at 12 hours; or between 0% to about 50% at 1 hour, from about 15% to about 70% at 2 hours, from about 20% to about 75% at 4 hours, from about 30% to about 80% at 6 hours, from about 30% to about 90% at 9 hours, and greater than about 70% at 12 hours; or between 0% to about 60% at 1 hour, from about 15% to about 80% at 2 hours, from about 25% to about 85% at 4 hours, from about 35% to about 90% at 6 hours, from about 40% to about 90% at 9 hours, and greater than about 80% at 12 hours; ; or between 0% to about 70% at 1 hour, from about 20% to about 80% at 2 hours, from about 25% to about 80% at 4 hours, from about 35% to about 80% at 6 hours, from about 40% to about 80% at 9 hours, and greater than about 60% at 12 hours; or between 0% to about 75% at

1 hour, from about 30% to about 80% at 2 hours, from about 35% to about 90% at 4 hours, from about 50% to about 90% at 6 hours, from about 55% to about 95% at 9 hours, and greater than about 70% at 12 hours.

[00334] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release rate by weight of the cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours. In other preferred embodiments, said release rate is between 2% and about 50% at 1 hour, between about 5% and about 75% at 2 hours, between about 15% and about 75% at 4 hours, between about 30% and about 90% at 8 hours, greater than about 40% at 12 hours, greater than about 60% at 18 hours, and greater than about 70% at 24 hours; or between 1% and about 40% at 1 hour, between about 2% and about 60% at 2 hours, between about 10% and about 65% at 4 hours, between about 20% and about 80% at 8 hours, greater than about 30% at 12 hours, greater than about 40% at 18 hours, and greater than about 60% at 24 hours; or between 5% and about 60% at 1 hour, between about 15% and about 80% at 2 hours, between about 25% and about 95% at 4 hours, between about 45% and about 100% at 8 hours, greater than about 60% at 12 hours, greater than about 80% at 18 hours, and greater than about 90% at 24 hours; or between 10% and about 65% at 1 hour, between about 20% and about 85% at 2 hours, between about 30% and about 100% at 4 hours, between about 60% and about 100% at 8 hours, greater than about 70% at 12 hours, greater than about 90% at 18 hours, and greater than about 95% at 24 hours.

[00335] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release rate by weight of the cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% to about 30% at 1 hour, from about 10% to about 65% at 4 hours, from about 20% to about 70% at 8 hours, from about 25% to about 80% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours. In other preferred embodiments, said release rate is between 0% to about 20% at 1 hour, from about 5% to about 50% at 4 hours, from about 10% to about 60% at 8 hours, from about 15% to about 70% at 12 hours, from about 25% to about 90% at 18 hours, and greater than about 55% at 24 hours; or between 0% to about 10% at 1 hour, from about 5% to about 40% at 4 hours, from about 8% to about 50% at 8 hours, from about 10% to about 60% at 12 hours, from about 22% to about 80% at 18 hours, and greater than about 45% at 24 hours; or between 0% to about 35% at 1 hour, from about 15% to about 70% at 4 hours, from about 25% to about 75% at 8 hours, from about 30% to about 85% at 12 hours, from about 40% to about 100% at 18 hours, and greater than about 75% at 24 hours; or between 0% to about 40% at 1 hour, from about 20% to about 70% at 4 hours, from about 30% to about 80% at 8 hours, from about 35% to about 90% at 12 hours, from about 45% to about 100% at 18 hours, and greater than about 80% at 24 hours; or between 0% to about 45% at 1 hour, from about 25% to about 75% at 4 hours, from about 35% to about 85% at 8 hours, from about 40% to about 90% at 12 hours, from about 50% to about 100% at 18 hours, and greater than about 90% at 24 hours; or between 0% to about 50% at 1 hour, from about 30% to about 80% at 4 hours, from about 40% to about 90% at 8 hours, from about 45% to about 95% at 12 hours, from about 60% to about 100% at 18 hours, and greater than about 95% at 24 hours; or between 0% to about 60% at 1 hour, from about 40% to about 80% at 4 hours, from about 45% to about

90% at 8 hours, from about 50% to about 100% at 12 hours, from about 70% to about 100% at 18 hours, and greater than about 80% at 24 hours.

[00336] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release rate by weight of the cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 25% and about 100% at 12 hours, between about 30% and about 100% at 16 hours, between about 50% and about 100% at 24 hours, and greater than about 80% at 36 hours. In other preferred embodiments, said release rate is between 0% and about 40% at 1 hour, between about 0% and about 65% at 2 hours, between about 2% and about 85% at 4 hours, between about 8% and about 90% at 8 hours, between about 20% and about 95% at 12 hours, between about 25% and about 95% at 16 hours, between about 40% and about 90% at 24 hours, and greater than about 70% at 36 hours; or between 0% and about 30% at 1 hour, between about 0% and about 50% at 2 hours, between about 1% and about 75% at 4 hours, between about 5% and about 80% at 8 hours, between about 10% and about 85% at 12 hours, between about 15% and about 90% at 16 hours, between about 30% and about 80% at 24 hours, and greater than about 70% at 36 hours; or between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 5% and about 100% at 4 hours, between about 15% and about 100% at 8 hours, between about 35% and about 100% at 12 hours, between about 40% and about 100% at 16 hours, between about 60% and about 100% at 24 hours, and greater than about 85% at 36 hours; or between 0% and about 65% at 1 hour, between about 0% and about 85% at 2 hours, between about 10% and about 100% at 4 hours, between about 20% and about 100% at 8 hours, between about 40% and about

100% at 12 hours, between about 50% and about 100% at 16 hours, between about 70% and about 100% at 24 hours, and greater than about 90% at 36 hours; or between 0% and about 70% at 1 hour, between about 0% and about 90% at 2 hours, between about 20% and about 100% at 4 hours, between about 30% and about 100% at 8 hours, between about 50% and about 100% at 12 hours, between about 60% and about 100% at 16 hours, between about 80% and about 100% at 24 hours, and greater than about 95% at 36 hours.

[00337] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release rate by weight of the cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 20% and about 50% at 1 hour, between about 40% and about 75% at 2 hours, between about 60% and about 95% at 4 hours, between about 80% and about 100% at 8 hours and between about 90% and about 100% at 12 hours. In other preferred embodiments, said release rate is between 15% and about 45% at 1 hour, between about 35% and about 70% at 2 hours, between about 55% and about 90% at 4 hours, between about 75% and about 90% at 8 hours and between about 80% and about 95% at 12 hours; or between 10% and about 40% at 1 hour, between about 30% and about 65% at 2 hours, between about 50% and about 85% at 4 hours, between about 70% and about 85% at 8 hours and between about 75% and about 90% at 12 hours; or between 5% and about 35% at 1 hour, between about 25% and about 60% at 2 hours, between about 45% and about 80% at 4 hours, between about 65% and about 80% at 8 hours and between about 70% and about 85% at 12 hours; or between 25% and about 55% at 1 hour, between about 45% and about 80% at 2 hours, between about 65% and about 95% at 4 hours, between about 85% and about 100% at 8 hours and between about 95% and about 100% at 12 hours; or between 30% and about 60% at 1 hour, between about 50% and about 80% at 2 hours, between about 70% and about 95% at 4 hours, between

about 90% and about 100% at 8 hours and between about 95% and about 100% at 12 hours; or between 35% and about 60% at 1 hour, between about 50% and about 80% at 2 hours, between about 80% and about 95% at 4 hours, between about 90% and about 100% at 8 hours and between about 95% and about 100% at 12 hours; or between 20% and about 40% at 1 hour, between about 40% and about 65% at 2 hours, between about 60% and about 85% at 4 hours, between about 70% and about 90% at 8 hours and between about 80% and about 100% at 12 hours.

[00338] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release rate by weight of the cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 10% and about 95% at 4 hours, between about 35% and about 100% at 8 hours, between about 55% and about 100% at 12 hours, between about 70% to about 100% at 16 hours, and greater than about 90% at 24 hours. In other preferred embodiments, said release rate is between 0% and about 40% at 1 hour, between about 0% and about 65% at 2 hours, between about 8% and about 85% at 4 hours, between about 30% and about 90% at 8 hours, between about 45% and about 100% at 12 hours, between about 60% to about 100% at 16 hours, and greater than about 80% at 24 hours; or between 0% and about 30% at 1 hour, between about 0% and about 55% at 2 hours, between about 5% and about 75% at 4 hours, between about 20% and about 80% at 8 hours, between about 35% and about 100% at 12 hours, between about 50% to about 100% at 16 hours, and greater than about 70% at 24 hours; or between 0% and about 20% at 1 hour, between about 0% and about 45% at 2 hours, between about 5% and about 65% at 4 hours, between about 10% and about 70% at 8 hours, between about 25% and about 80% at 12 hours, between about 40% to about 100% at 16 hours, and

greater than about 60% at 24 hours; or between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 15% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, between about 60% and about 100% at 12 hours, between about 75% to about 100% at 16 hours, and greater than about 90% at 24 hours; or between 0% and about 65% at 1 hour, between about 0% and about 85% at 2 hours, between about 20% and about 90% at 4 hours, between about 45% and about 100% at 8 hours, between about 65% and about 100% at 12 hours, between about 80% to about 100% at 16 hours, and greater than about 90% at 24 hours; or between 0% and about 40% at 1 hour, between about 0% and about 50% at 2 hours, between about 10% and about 80% at 4 hours, between about 25% and about 70% at 8 hours, between about 40% and about 80% at 12 hours, between about 60% to about 100% at 16 hours, and greater than about 90% at 24 hours.

[00339] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release rate by weight of the cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% and about 30% at 1 hour, between about 0% and about 45% at 2 hours, between about 3% and about 55% at 4 hours, between about 10% and about 65% at 8 hours, between about 20% and about 75% at 12 hours, between about 30% to about 88% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours. In other preferred embodiments, said release rate is between 0% and about 25% at 1 hour, between about 0% and about 40% at 2 hours, between about 2% and about 50% at 4 hours, between about 8% and about 60% at 8 hours, between about 10% and about 70% at 12 hours, between about 25% to about 80% at 16 hours, between about 45% and about 100% hours at 24 hours and greater than 75% at 36 hours; or between 0% and about 20% at 1 hour, between about 0% and about 35% at 2 hours, between about 1% and about 45% at 4 hours,

between about 5% and about 55% at 8 hours, between about 8% and about 65% at 12 hours, between about 20% to about 75% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 70% at 36 hours; or between 0% and about 15% at 1 hour, between about 0% and about 30% at 2 hours, between about 0% and about 40% at 4 hours, between about 5% and about 50% at 8 hours, between about 8% and about 60% at 12 hours, between about 15% to about 70% at 16 hours, between about 35% and about 100% hours at 24 hours and greater than 60% at 36 hours; or between 0% and about 10% at 1 hour, between about 0% and about 25% at 2 hours, between about 0% and about 35% at 4 hours, between about 5% and about 45% at 8 hours, between about 10% and about 50% at 12 hours, between about 10% to about 60% at 16 hours, between about 30% and about 90% hours at 24 hours and greater than 70% at 36 hours; or between 0% and about 35% at 1 hour, between about 0% and about 50% at 2 hours, between about 5% and about 60% at 4 hours, between about 15% and about 70% at 8 hours, between about 25% and about 80% at 12 hours, between about 35% to about 90% at 16 hours, between about 55% and about 100% hours at 24 hours and greater than 85% at 36 hours; or between 0% and about 40% at 1 hour, between about 0% and about 55% at 2 hours, between about 10% and about 65% at 4 hours, between about 20% and about 75% at 8 hours, between about 30% and about 85% at 12 hours, between about 40% to about 100% at 16 hours, between about 55% and about 100% hours at 24 hours and greater than 90% at 36 hours; or between 0% and about 45% at 1 hour, between about 0% and about 60% at 2 hours, between about 15% and about 70% at 4 hours, between about 25% and about 80% at 8 hours, between about 35% and about 90% at 12 hours, between about 45% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 60% at 36 hours; or between 0% and about 50% at 1 hour, between about 5% and about 65% at 2 hours, between about 20% and about 75% at 4 hours, between about 30% and about 85% at 8 hours, between about 40% and about 95% at 12 hours, between about 50% to about 100% at 16 hours, between about 70% and about 100%

hours at 24 hours and greater than 70% at 36 hours; or between 0% and about 30% at 1 hour, between about 5% and about 40% at 2 hours, between about 10% and about 60% at 4 hours, between about 20% and about 70% at 8 hours, between about 30% and about 100% at 12 hours, between about 40% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 90% at 36 hours; or between 0% and about 30% at 1 hour, between about 0% and about 30% at 2 hours, between about 0% and about 30% at 4 hours, between about 5% and about 70% at 8 hours, between about 10% and about 80% at 12 hours, between about 20% to about 100% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 50% at 36 hours; or between 0% and about 20% at 1 hour, between about 0% and about 20% at 2 hours, between about 0% and about 20% at 4 hours, between about 0% and about 20% at 8 hours, between about 5% and about 40% at 12 hours, between about 10% to about 80% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 60% at 36 hours; or between 0% and about 10% at 1 hour, between about 0% and about 20% at 2 hours, between about 0% and about 40% at 4 hours, between about 5% and about 60% at 8 hours, between about 10% and about 80% at 12 hours, between about 20% to about 100% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 50% at 36 hours.

**[00340]** In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release rate by weight of the cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 20% and about 100% at 12 hours, between about 30% to about 100% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36

hours. In other preferred embodiments, said release rate is between 0% and about 45% at 1 hour, between about 0% and about 70% at 2 hours, between about 3% and about 90% at 4 hours, between about 8% and about 100% at 8 hours, between about 15% and about 100% at 12 hours, between about 25% to about 100% at 16 hours, between about 45% and about 100% hours at 24 hours and greater than 80% at 36 hours; or between 0% and about 40% at 1 hour, between about 0% and about 65% at 2 hours, between about 0% and about 80% at 4 hours, between about 5% and about 80% at 8 hours, between about 10% and about 90% at 12 hours, between about 20% to about 100% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 70% at 36 hours; or between 0% and about 35% at 1 hour, between about 0% and about 60% at 2 hours, between about 0% and about 70% at 4 hours, between about 3% and about 70% at 8 hours, between about 5% and about 80% at 12 hours, between about 15% to about 100% at 16 hours, between about 30% and about 100% hours at 24 hours and greater than 40% at 36 hours; or between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 5% and about 100% at 4 hours, between about 15% and about 100% at 8 hours, between about 30% and about 100% at 12 hours, between about 40% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 70% at 36 hours; or between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 5% and about 95% at 4 hours, between about 25% and about 80% at 8 hours, between about 30% and about 100% at 12 hours, between about 40% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 60% at 36 hours; or between 0% and about 60% at 1 hour, between about 0% and about 85% at 2 hours, between about 5% and about 100% at 4 hours, between about 10% and about 100% at 8 hours, between about 20% and about 100% at 12 hours, between about 30% to about 100% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours.

[00341] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said cannabinoid agonist dosage form providing an in-vitro release rate by weight of the cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 15% and about 25% at 1 hour, between about 25% and about 35% at 2 hours, between about 30% and about 45% at 4 hours, between about 40% and about 60% at 8 hours, between about 55% and about 70% at 12 hours and between about 60% to about 75% at 16 hours. In other preferred embodiments, said release rate is between 10% and about 20% at 1 hour, between about 20% and about 30% at 2 hours, between about 25% and about 40% at 4 hours, between about 30% and about 50% at 8 hours, between about 50% and about 65% at 12 hours and between about 55% to about 65% at 16 hours; or between 5% and about 15% at 1 hour, between about 15% and about 25% at 2 hours, between about 20% and about 35% at 4 hours, between about 25% and about 45% at 8 hours, between about 45% and about 60% at 12 hours and between about 50% to about 60% at 16 hours; or between 15% and about 30% at 1 hour, between about 20% and about 40% at 2 hours, between about 20% and about 50% at 4 hours, between about 30% and about 70% at 8 hours, between about 60% and about 80% at 12 hours and between about 70% to about 90% at 16 hours; or between 0% and about 50% at 1 hour, between about 5% and about 50% at 2 hours, between about 5% and about 70% at 4 hours, between about 10% and about 80% at 8 hours, between about 20% and about 100% at 12 hours and between about 40% to about 100% at 16 hours; or between 15% and about 40% at 1 hour, between about 15% and about 45% at 2 hours, between about 20% and about 60% at 4 hours, between about 20% and about 80% at 8 hours, between about 30% and about 90% at 12 hours and between about 40% to about 100% at 16 hours.

[00342] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of

cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said in-vitro release rate being substantially independent of pH in that a difference, at any given time, between an amount of cannabinoid agonist released at one pH and an amount released at any other pH, when measured in-vitro using the USP Basket or Paddle Method of USP Drug Release test of U.S. Pharmacopeia (2003) at 100 rpm in 900 ml aqueous buffer, is no greater than 30%. In other preferred embodiments, the difference, at any given time, between an amount of cannabinoid agonist released at one pH and an amount released at any other pH using the aforementioned methods is no greater than 50%, or no greater than 40%, or no greater than 35%, or no greater than 25%, or no greater than 20%, or no greater than 15%, or no greater than 10%, or no greater than 5%.

[00343] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said dosage forms of cannabinoid agonist providing in-vitro release rates by weight of between 0% to about 50% by weight of the cannabinoid agonist from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 700 ml of Simulated Gastric Fluid (SGF) at 37 °C. In other preferred embodiments, said release rate at one hour is between 0% to about 10% by weight, or 0% to about 20% by weight, or is between 0% to about 30% by weight, or 0% to about 40% by weight, or between 0% to about 60% by weight, or 0% to about 70% by weight, or 0% to about 80% by weight, or 0% to about 90% by weight, or 10% to about 50% by weight, or 10% to about 60% by weight, or 10% to about 70% by weight, or 10% to about 90% by weight, or 10% to about 100% by weight, or 30% to about 100% by weight, or 50% to about 100% by weight.

[00344] In some preferred embodiments, the dosage form provides a pharmaceutical composition comprising a therapeutically effective amount of cannabinoid agonist or pharmaceutically acceptable salts thereof or mixtures thereof, said dosage forms of cannabinoid agonist providing in-vitro release

rates by weight of cannabinoid agonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of between 0% to about 80% at 0.5 hours, and greater than about 40% at 1 hour. In other preferred embodiments, said release rate is between 0% to about 40% at 0.5 hours, and greater than about 60% at 1 hour; or between 0% to about 20% at 0.5 hours, and greater than about 40% at 1 hour; or between 0% to about 20% at 0.5 hours, and greater than about 20% at 1 hour; or between 0% to about 90% at 0.5 hours, and greater than about 60% at 1 hour; or between 0% to about 100% at 0.5 hours, and greater than about 60% at 1 hour; or between 0% to about 90% at 1 hour, and greater than about 40% at 2 hours; or between 0% to about 100% at 1 hour, and greater than about 60% at 2 hours; or between 0% to about 60% at 1 hour, and greater than about 40% at 2 hours; or between 0% to about 40% at 1 hour, and greater than about 30% at 2 hours; or between 0% to about 50% at 1 hour, and greater than about 40% at 2 hours; or between 0% to about 30% at 1 hour, and greater than about 20% at 2 hours; or between 0% and about 50% at 1 hour, between about 0% and about 80% at 2 hours, between about 5% and about 100% at 4 hours and between about 10% and about 100% at 8 hours; or between 10% and about 60% at 1 hour, between about 15% and about 75% at 2 hours, between about 20% and about 95% at 4 hours and between about 30% and about 100% at 8 hours.

[00345] In some preferred embodiments, some or all of the dissolution embodiments and specifications (e.g., USP Basket Method, USP Paddle Method) of the invention applicable to the cannabinoid agonist of the oral dosage are also applicable to the releasable or substantially releasable opioid antagonist of the dosage form. In the interest of brevity, said opioid antagonist dissolution embodiments and specifications are not repeated.

[00346] In some preferred embodiments, some or all of the pharmacokinetic embodiments and specifications (e.g., $C_{max}$, $T_{max}$, AUC, percent absorption) of the invention applicable to the cannabinoid agonist of the oral dosage are also applicable to the releasable or substantially releasable opioid antagonist of the

dosage form. In the interest of brevity, said pharmacokinetic embodiments and specifications are not repeated.

**Alkylcellulose Polymers**

[00347] Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

[00348] One commercially-available aqueous dispersion of ethylcellulose is Aquacoat. Aquacoat is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat with a suitable plasticizer prior to use.

[00349] Another aqueous dispersion of ethylcellulose is commercially available as Surelease. This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

**Acrylic Polymers**

[00350] In other preferred embodiments of the present invention, the hydrophobic material comprising the controlled release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic

acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[00351] In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

[00352] In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

[00353] Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit. There are several different types of Eudragit. For example, Eudragit E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit RL and Eudragit RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit RL and RS are pH-independent.

[00354] In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from under the trade names Eudragit RL30D and Eudragit RS30D, respectively. Eudragit RL30D and Eudragit RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of

ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit RL30D and 1:40 in Eudragit RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

[00355] The Eudragit RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit RL, 50% Eudragit RL and 50% Eudragit RS, and 10% Eudragit RL:90%Eudragit RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit L.

**Plasticizers**

[00356] In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

[00357] Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

[00358] Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

[00359] It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

**Processes for Preparing Coated Beads**

[00360] When a hydrophobic controlled release coating material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, which are already coated with the cannabinoid agonist, opioid antagonist or cannabinoid agonist plus opioid antagonist (hereinafter referred to as cannabinoid agonist/opioid antagonist), a plurality of the resultant solid controlled release beads may thereafter be placed in a gelatin capsule. The dosage form provides an effective controlled release dose of the cannabinoid agonist/opioid antagonist when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

[00361] The controlled release bead formulations of the present invention slowly release the cannabinoid agonist/opioid antagonist, e.g., when ingested

and exposed to gastric fluids, and then to intestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which the plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

[00362] Spheroids or beads coated with a cannabinoid agonist/opioid antagonist may be prepared, e.g., by dissolving the drug in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the cannabinoid agonist/opioid antagonist to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropyl methylcellulose, etc. with or without colorant (e.g., Opadry) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropyl methylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

[00363] The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat or Surelease, may be used. If Surelease is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit can be used.

[00364] The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color may be added to Aquacoat via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

[00365] Plasticized hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined controlled release of said therapeutically active agent when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

[00366] The release of the therapeutically active agent from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The

ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

[00367] The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropyl methylcellulose.

[00368] The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

[00369] The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain. The release-modifying agent may also comprise a semi-permeable polymer. In certain preferred embodiments, the release-modifying agent is selected from hydroxypropyl methylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

[00370] The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 4,063,064 and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

**Matrix Formulations**

[00371] In other embodiments of the present invention, the controlled release formulation is achieved via a matrix having a controlled release coating as set forth above. The present invention also comprises sustained-release tablets comprising a cannabinoid agonist and opioid antagonist, wherein the agonist and the antagonist are dispersed in a controlled release matrix that affords in-vitro dissolution rates of the cannabinoid agonist/opioid antagonist within the preferred ranges and that releases the cannabinoid agonist in a pH-dependent

or pH-independent manner. The materials suitable for inclusion in a controlled release matrix will depend on the method used to form the matrix.

[00372] For example, a matrix in addition to the cannabinoid agonist/opioid antagonist, may include: (i) Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials; the list is not meant to be exclusive, and any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting controlled release of the cannabinoid agonist/opioid antagonist may be used in accordance with the present invention; (ii) Digestible, long chain ($C_8$ -$C_{50}$, especially $C_{12}$-$C_{40}$), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols.

[00373] Of these polymers, especially Eudragit RSPO, the cellulose ethers, especially hydroxyalkyl celluloses and carboxyalkyl celluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

[00374] When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25°C and 90°C. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

[00375] Preferably, the oral dosage form contains up to 60% (by weight) of at least one polyalkylene glycol.

[00376] The hydrophobic material is preferably selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer,

poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

[00377] Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 30°C to about 200°C, preferably from about 45°C to about 90°C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic aid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and camauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30°C to about 100°C.

[00378] Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain ($C_8$-$C_{50}$, especially $C_{12}$-$C_{40}$), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25°C and 90°C are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

[00379] Preferably, a combination of two or more hydrophobic materials are included in the matrix formulations. If an additional hydrophobic material is

included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

[00380] One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one $C_{12}$-$C_{36}$, preferably $C_{14}$-$C_{22}$, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy ($C_1$ to $C_6$) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of cannabinoid release required. The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of cannabinoid agonist/opioid antagonist release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

[00381] In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the cannabinoid agonist/opioid antagonist from the formulation. A ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol

of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

[00382] The at least one polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1,000 and 15,000 especially between 1,500 and 12,000.

[00383] Another suitable controlled release matrix would comprise an alkylcellulose (especially ethyl cellulose), a $C_{12}$ to $C_{36}$ aliphatic alcohol and, optionally, a polyalkylene glycol.

[00384] In another preferred embodiment, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials.

[00385] In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

**Processes for Preparing Matrix--Based Beads**

[00386] In order to facilitate the preparation of a solid, controlled release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and cannabinoid or a cannabinoid salt; (b) mixing the hydroxyalkyl cellulose containing granules with at least one $C_{12}$-$C_{36}$ aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxy-alkyl cellulose plus cannabinoid agonist/opioid antagonist with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the cannabinoid.

[00387] In yet other alternative embodiments, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101. In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

**Melt Extrusion Matrix**

[00388] Sustained release matrices can also be prepared via melt-granulation or melt-extrusion techniques, as long as the techniques. Alternatively, the melt extrusion step may be performed with the cannabinoid agonist/opioid antagonist to produce sustained release particles. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Pat. No. 4,861,598, and hereby incorporated by reference in its entirety.

[00389] The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant

release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

[00390] In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

[00391] In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired.

[00392] Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

**Melt Extrusion Multiparticulates**

[00393] The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the cannabinoid agonist/opioid antagonist, together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and

provides sustained release of the cannabinoid agonist/opioid antagonist for a time period of from about 6 to about 24 hours.

[00394] An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, a therapeutically active agent, and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm.

[00395] The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

[00396] The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic material as described herein. In this regard, the melt-extruded multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

[00397] In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastric fluid.

[00398] In another preferred embodiment, a suitable amount of the multiparticulate extrudate compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, incorporated by reference herein.

[00399] Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2 to about 30 percent, although the overcoat may be greater depending upon the physical properties of the particular cannabinoid compound utilized and the desired release rate, among other things.

[00400] The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded multiparticulates containing one or more of the therapeutically active agents disclosed above before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release cannabinoid agonist for prompt therapeutic effect and optionally, an immediate release amount of the opioid antagonist. The immediate release cannabinoid agonist may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the multiparticulates after preparation of the dosage forms (e.g., controlled release coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of controlled release beads and matrix multiparticulates to achieve a desired effect.

[00401] The sustained release formulations of the present invention preferably slowly release the cannabinoid agonist and/or the opioid antagonist e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e.,

hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

[00402] In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the cannabinoid agonist and/or opioid antagonist particles, which are added thereafter to the extrudate. Such formulations typically will have the drugs blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release of the cannabinoid agonist. Such formulations may be advantageous, for example, when the therapeutically active agent included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

**Detailed Descriptions of the Preferred Embodiments**

[00403] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

[00404] Other suitable releasable cannabinoid agonists and releasable or substantially opioid antagonists, as defined in this invention may also be prepared by modification of the examples herein and by use of material other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

[00405] Other suitable immediate release and controlled release dosage forms of releasable cannabinoid agonists and releasable or substantially opioid antagonists as defined in this invention may also be prepared by modification of the examples herein and by use of material other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

[00406] Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

[00407] A wide variety of materials can be used for preparing the dosage form according to this invention. This invention therefore contemplates the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

[00408] A wide variety of methods known in the art for the preparation of immediate release and controlled release dosage forms may be incorporated into the invention.

[00409] More than one releasable cannabinoid agonist and releasable or substantially opioid antagonist may be included in the dosage form either in the form of separate subunits, on combined into the same subunit.

[00410] Abuse intervention agents may optionally be incorporated into the same sub-unit as the releasable cannabinoid agonists and releasable or substantially opioid antagonists or into a different sub-unit or into the granulation or matrix material containing the releasable cannabinoid agonists and releasable or substantially opioid antagonists.

[00411] The percent loading of the releasable cannabinoid agonists and releasable or substantially opioid antagonists and the abuse intervention agent onto the beads may be varied depending on the physiochemical and pharmaceutical properties of said agent and ingredients (excipients), the pharmacologic effects of said agent and the desired rate and extent of release from the dosage form.

[00412] When the opioid antagonist is in the form of multiparticulates, it may be directly or indirectly be overcoated with the cannabinoid agonist such that each multiparticulate contains releasable cannabinoid agonists and releasable or substantially opioid antagonists, and filled uncompressed into a capsule or compressed into a capsule or tablet.

[00413] When the cannabinoid agonist is in the form of multiparticulates, it may be directly or indirectly be overcoated with the opioid antagonist such that each multiparticulate contains releasable cannabinoid agonists and

releasable or substantially opioid antagonists, and filled uncompressed into a capsule or compressed into a capsule or tablet.

[00414] The ingredients used for the preparation of the releasable cannabinoid agonists and releasable or substantially opioid antagonists in immediate release form or controlled release form may be modified depending on the selection, dose and desired duration of effect of the releasable cannabinoid agonists and releasable or substantially opioid antagonists. In some embodiments, a change in the dose or amount releasable cannabinoid agonists and releasable or substantially opioid antagonists will not require a change in amount of other ingredients. In other embodiments, a proportional change in the amount of other ingredients will be required to maintain the desired properties. In yet other embodiments, a change in the dose or amount releasable cannabinoid agonists and releasable or substantially opioid antagonists will necessitate a change in the nature and/or amount of ingredients to provide the required characteristics of the releasable cannabinoid agonists and releasable or substantially opioid antagonists (e.g., immediate release, sustained release, duration of effect, rate and extent of absorption, therapeutic concentrations and effect, degree and duration of abuse deterrence, etc).

[00415] EXAMPLE 1

| | **Ingredients** | **Amount/Unit** |
|---|---|---|
| 1 | Nabilone | 2 mg |
| 2 | Polyvinylpyrrolidine | 7.5 mg |
| 3 | Lactose | 30 mg |
| 4 | Alcohol SD3A-2 proof | 3 mL |
| 5 | Stearic acid | 5 mg |
| 6 | Talc | 7.5 mg |
| 7 | Cornstarch | 20 mg |
| 8 | Naltrexone | 5 mg |

[00416] Blend 1, 2, 3 and 8 together; pass through a 40-mesh screen. Add 4 slowly and knead well. Screen wet mass through a 4-mesh screen. Dry the granulation at 50 °C overnight. Screen the dried granulation through a 20-mesh screen. Bolt 5, 6 and 7 through a 60-mesh screen prior to mixing by tumbling with granulation. Tumble and mix contents and compress using a tablet punch. Film coat as desired.

[00417] In some embodiments, the compressed tablets can be formulated using conventional dry granulation procedures and equipment. In other embodiments, the uncompressed granulate can be filled in a hard shell capsule.

EXAMPLE 2

[00418] See procedure outlined in Example 1.

| | **Ingredients** | **Amount/Unit** |
|---|---|---|
| 1 | Dronabinol | 2.5 mg |
| 2 | Polyvinylpyrrolidine | 7.5 mg |
| 3 | Lactose | 30 mg |
| 4 | Alcohol SD3A-2 proof | 3 mL |
| 5 | Stearic acid | 5 mg |
| 6 | Talc | 7.5 mg |
| 7 | Cornstarch | 20 mg |
| 8 | Naloxone | 4 mg |

EXAMPLE 3

[00419] See procedure outlined in Example 1.

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | delta-9-tetrahydrocannabinol (THC) | 25 mg |
| 2 | Polyvinylpyrrolidine | 7.5 mg |
| 3 | Lactose | 30 mg |
| 4 | Alcohol SD3A-2 proof | 3 mL |
| 5 | Stearic acid | 5 mg |
| 6 | Talc | 7.5 mg |
| 7 | Cornstarch | 20 mg |
| 8 | Naltrexone | 5 mg |

EXAMPLE 4

[00420] See procedure outlined in Example 1.

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | delta-9-tetrahydrocannabinol (THC) | 100 mg |
| 2 | Polyvinylpyrrolidine | 7.5 mg |
| 3 | Lactose | 30 mg |
| 4 | Alcohol SD3A-2 proof | 3 mL |
| 5 | Stearic acid | 5 mg |
| 6 | Talc | 7.5 mg |
| 7 | Cornstarch | 20 mg |
| 8 | Naloxone | 5 mg |

EXAMPLE 5

[00421] See procedure outlined in Example 1.

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | Cannabidiol | 25 mg |
| 2 | Polyvinylpyrrolidine | 7.5 mg |
| 3 | Lactose | 30 mg |
| 4 | Alcohol SD3A-2 proof | 3 mL |
| 5 | Stearic acid | 5 mg |
| 6 | Talc | 7.5 mg |
| 7 | Cornstarch | 20 mg |
| 8 | Nalmefene | 5 mg |

EXAMPLE 6

[00422] See procedure outlined in Example 1.

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | Cannabidiol | 100 mg |
| 2 | Polyvinylpyrrolidine | 7.5 mg |
| 3 | Lactose | 30 mg |
| 4 | Alcohol SD3A-2 proof | 3 mL |
| 5 | Stearic acid | 5 mg |
| 6 | Talc | 7.5 mg |
| 7 | Cornstarch | 20 mg |
| 8 | Naltrexone | 10 mg |

[00423] EXAMPLE 7

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | Nabilone | 2 mg |
| 2 | Lactose (granular, 12 mesh) | 25 mg |
| 3 | Starch | 20 mg |
| 4 | Talc | 20 mg |

| | | |
|---|---|---|
| 5 | Magnesium Stearate | 0.3 mg |
| 6 | Naloxone | 5 mg |

[00424] Mix ingredients 1 to 6 thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Compress into tablets using a punch. Film coat as desired. In some embodiments, the uncompressed granulate can be filled in a hard shell capsule.

[00425] EXAMPLE 8

| | **Ingredients** | **Amount/Unit** |
|---|---|---|
| 1 | Dronabinol | 2.5 mg |
| 2 | Lactose (granular, 12 mesh) | 25 mg |
| 3 | Starch | 20 mg |
| 4 | Talc | 20 mg |
| 5 | Magnesium Stearate | 0.3 mg |
| 6 | Naltrexone | 2 mg |

[00426] See procedure outlined in Example 7.

[00427] EXAMPLE 9

| | **Ingredients** | **Amount/Unit** |
|---|---|---|
| 1 | delta-9-tetrahydrocannabinol (THC) | 25 mg |
| 2 | Lactose (granular, 12 mesh) | 50 mg |
| 3 | Starch | 30 mg |
| 4 | Talc | 25 mg |
| 5 | Magnesium Stearate | 0.5 mg |
| 6 | Naloxone | 2 mg |

[00428] See procedure outlined in Example 7.

[00429] EXAMPLE 10

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | delta-9-tetrahydrocannabinol (THC) | 100 mg |
| 2 | Lactose (granular, 12 mesh) | 100 mg |
| 3 | Starch | 40 mg |
| 4 | Talc | 35 mg |
| 5 | Magnesium Stearate | 0.8 mg |
| 6 | Naltrexone | 5 mg |

[00430] See procedure outlined in Example 7.

[00431] EXAMPLE 11

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | Cannabidiol | 25 mg |
| 2 | Lactose (granular, 12 mesh) | 50 mg |
| 3 | Starch | 30 mg |
| 4 | Talc | 25 mg |
| 5 | Magnesium Stearate | 0.5 mg |
| 6 | Naloxone | 8 mg |

[00432] See procedure outlined in Example 7.

[00433] EXAMPLE 12

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | Cannabidiol | 100 mg |
| 2 | Lactose (granular, 12 mesh) | 100 mg |
| 3 | Starch | 40 mg |
| 4 | Talc | 35 mg |
| 5 | Magnesium Stearate | 0.8 mg |
| 6 | Nalmefene | 10 mg |

[00434] See procedure outlined in Example 7.

[00435] EXAMPLE 13

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | Nabilone | 4 mg |
| 2 | HPMC 2208, USP | 150 mg |
| 3 | Carnauba wax | 30 mg |
| 4 | HPMC 2910, USP | 15 mg |
| 5 | Magnesium Stearate | 2 mg |
| 6 | Stearic acid | 8 mg |
| 7 | Talc | 3 mg |
| 8 | Naltrexone | 20 mg |

[00436] Place the ingredients 1, 2, 3 and 8 in the granulator and mix for 15 minutes. Dissolve ingredient 4 in water (mix in hot water, then cool down) and spay into the fluidized mixture. Dry to approximately 5% moisture. Sequentially add ingredient 5, 6 and 7, with mixing steps between each addition. Compress into tablets using a punch. Film coat as desired. In some embodiments, the uncompressed granulate can be filled in a hard shell capsule.

[0100] EXAMPLE 14

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | Dronabinol | 4 mg |
| 2 | HPMC 2208, USP | 150 mg |
| 3 | Carnauba wax | 30 mg |
| 4 | HPMC 2910, USP | 15 mg |
| 5 | Magnesium Stearate | 2 mg |
| 6 | Stearic acid | 8 mg |
| 7 | Talc | 3 mg |
| 8 | Naloxone | 10 mg |

[0101] See procedure outlined in Example 13.

[0102] EXAMPLE 15

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | delta-9-tetrahydrocannabinol | 25 mg |
| 2 | HPMC 2208, USP | 150 mg |
| 3 | Carnauba wax | 30 mg |
| 4 | HPMC 2910, USP | 15 mg |
| 5 | Magnesium Stearate | 2 mg |
| 6 | Stearic acid | 8 mg |
| 7 | Talc | 3 mg |
| 8 | Naloxone | 15 mg |

[00437] See procedure outlined in Example 13.

[00438] EXAMPLE 16

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | delta-9-tetrahydrocannabinol | 100 mg |
| 2 | HPMC 2208, USP | 150 mg |
| 3 | Carnauba wax | 30 mg |
| 4 | HPMC 2910, USP | 15 mg |
| 5 | Magnesium Stearate | 2 mg |
| 6 | Stearic acid | 8 mg |
| 7 | Talc | 3 mg |
| 8 | Naltrexone | 12 mg |

**[00439]** See procedure outlined in Example 13.

**[00440]** EXAMPLE 17

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | Cannabidiol | 25 mg |
| 2 | HPMC 2208, USP | 150 mg |
| 3 | Carnauba wax | 30 mg |
| 4 | HPMC 2910, USP | 15 mg |
| 5 | Magnesium Stearate | 2 mg |
| 6 | Stearic acid | 8 mg |
| 7 | Talc | 3 mg |
| 8 | Naltrexone | 15 mg |

**[00441]** See procedure outlined in Example 13.

**[00442]** EXAMPLE 18

| | Ingredients | Amount/Unit |
|---|---|---|
| 1 | Cannabidiol | 100 mg |
| 2 | HPMC 2208, USP | 150 mg |
| 3 | Carnauba wax | 30 mg |
| 4 | HPMC 2910, USP | 15 mg |
| 5 | Magnesium Stearate | 2 mg |
| 6 | Stearic acid | 8 mg |
| 7 | Talc | 3 mg |
| 8 | Naloxone | 10 mg |

[00443] See procedure outlined in Example 13.

[00444] A wide variety of methods are described in the art and herein for the preparation of controlled release dosage forms (e.g., tablets and capsule forms) of pharmaceuticals.

[00445] The cannabinoid agonist in controlled release form may be prepared separately from the opioid antagonists. The final dosage form containing the cannabinoid agonist and the opioid antagonists may be prepared by mixing the two forms and compressing it into a tablet and film coating as desired or filling into a capsule.

[00446] Alternatively the granulation comprising the cannabinoid agonist plus the opioid antagonists may be prepared together.

[00447] Example 19 to 36 are controlled release formulations of cannabinoid agonists plus opioid antagonists.

[00448] EXAMPLE 19

| Ingredients | Amt/Unit (mg) |
|---|---|
| delta-9-tetrahydrocannabinol (THC) | 30 |
| Naltrexone | 10 |
| Spray Dried Lactose | 60 |
| Povidone | 5 |
| Eudragit RS30D (solids) | 10 |
| Triacetin | 2 |
| Stearyl Alcohol | 25 |
| Talc | 2.5 |

| | |
|---|---|
| Magnesium Stearate | 1.25 |
| Opadry Pink Y-S-14518A | 4.0 |

[00449] 1. Granulation: Spray the Eudragit/Triacetin dispersion onto the THC, Naltrexone, Spray Dried Lactose and Povidone using a fluid bed granulator. 2. Milling: Discharge the granulation and pass through a mill. 3. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool. 4. Milling: Pass the cooled granulation through a mill. 5. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer. 6. Compression: Compress the granulation into tablets using a tablet press. 7. Film coating: Apply an aqueous film coat to the tablets.

[00450] EXAMPLE 20

| Ingredients | Amt/Unit (mg) |
|---|---|
| Cannabidiol | 30 |
| Naloxone | 5 |
| Eudragit RSPO | 76 |
| Eudragit RLPO | 4 |
| Stearyl Alcohol | 25 |

[00451] 1. Blend milled Stearyl Alcohol, Eudragit RLPO, Cannabidiol, Naloxone, and Eudragit RSPO using a Hobart Mixer. 2. Extrude the granulation using a Powder Feeder, Melt Extruder (equipped with the 6.times.1 mm die head), Conveyor, Lasermike, and Pelletizer. Powder feed rate-40 g/min; vacuum-.about 980 mBar; Conveyor, such that diameter of extrudate is 1 mm , Pelletizer, such that pellets are cut to 1 mm in length. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen. 4. Fill capsules with the pellets.

[00452] EXAMPLE 21

| Steps | Ingredients | Amt/unit (mg) |
|---|---|---|
| 1 | Dronabinol | 12 |
| | Naltrexone | 3 |
| | Non-pareil beads (30/35 mesh) | 45 |
| | Opadry Clear | 2.5 |

| | | |
|---|---|---|
| 2 | Eudragit RS3-D (dry) | 7.2 |
| | Eudragit RL30D (dry) | 0.4 |
| | Triethyl citrate | 1.5 |
| | Cabosil | 0.4 |
| 3 | Opadry Clear (HPMC) | 1.9 |
| | Cabosil | 0.28 |

[00453] 1. Dissolve Dronabinol, Naltrexone and Opadry (HPMC) in water. Spray the drug solution onto nonpareil beads in a fluid bed coater with Wurster insert. 2. Disperse Eudragit RS, Eudragit RL, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater. 3. Dissolve Opadry in water. Spray the solution onto the beads in the fluid bed coater. 4. Cure the beads at 60.degree. C. for 24 hours.

[00454] EXAMPLE 22

| Ingredients | Amt/Unit (mg) |
|---|---|
| Nabilone | 12 |
| Naloxone | 5 |
| Eudragit RSPO | 77 |
| Ethocel | 4.5 |
| Stearic acid | 27 |

[00455] 1. Blend milled Stearic acid, ethocel, Nabilone, Nalosone, and Eudragit RSPO using a V-blender. 2. Extrude the mixture using a Powder Feeder, Melt Extruder (equipped with the 6.times.1 mm die head), Conveyor, Lasermike, and Pelletizer. Powder feed rate, 1.2 kg/hr; vacuum, about.980 mBar; Conveyor, such that diameter of extrudate is 1 mm; Pelletizer, such that pellets are cut to 1 mm in length. 3. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen. Fill pellets in capsules.

[00456] Examples 23 to 27. 1. Pass the Stearyl Alcohol flakes through an occillating mill. 2. Mix the specified cannabinoid agonist, opioid antagonist, milled Stearyl Alcohol, Anhydrous Dicalcium Phosphate, Microcrystalline Cellulose, and Glyceryl Behenate in a twin shell blender. 3. Continuously feed the blended material into a twin screw extruder and collect the resultant heated

material on a conveyor. 4. Allow the extrudate to cool on the conveyor. 5. Mill the cooled extrudate using an occillating mill. 6. Blend the milled extrudate, and Magnesium Stearate. 6. Compress the resultant granulation using a tablet press, preferably into a caplet. 7. Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet.

[00457] EXAMPLE 23

| Ingredient | Amt/unit (mg) |
|---|---|
| THC | 30 |
| Naloxone | 20 |
| Anhydrous Dicalcium | 44 |
| Phosphate (Powdered) | 62 |
| Microcrystalline Cellulose | 62 |
| Glyceryl Behenate | 20 |
| Magnesium Stearate | 2 |
| Opadry Red | 10 |
| Purified Water | 57* |

*Remains in product as residual moisture only.

[00458] EXAMPLE 24

| Ingredient | Amt/unit (mg) |
|---|---|
| Nabilone | 30 |
| Nltrexone | 30 |
| Anhydrous Dicalcium | 44 |
| Phosphate (Powdered) | 62 |
| Microcrystalline Cellulose | 62 |
| Glyceryl Behenate | 20 |
| Magnesium Stearate | 2 |
| Opadry Red | 10 |
| Purified Water | 57* |

*Remains in product as residual moisture only.

[00459] EXAMPLE 25

| Ingredient | Amt/unit (mg) |
|---|---|
| Cannabidiol | 30 |
| Naltrexone | 15 |
| Anhydrous Dicalcium | 44 |

| | |
|---|---|
| Phosphate (Powdered) | 62 |
| Microcrystalline Cellulose | 62 |
| Glyceryl Behenate | 20 |
| Magnesium Stearate | 2 |
| Opadry Red | 10 |
| Purified Water | 57* |

*Remains in product as residual moisture only.

[00460] EXAMPLE 26

| Ingredient | Amt/unit (mg) |
|---|---|
| THC | 90 |
| Naloxone | 40 |
| Anhydrous Dicalcium | 130 |
| Phosphate (Powdered) | 180 |
| Microcrystalline Cellulose | 180 |
| Glyceryl Behenate | 60 |
| Magnesium Stearate | 6 |
| Opadry Red | 30 |
| Purified Water | 170* |

*Remains in product as residual moisture only.

[00461] EXAMPLE 27

| Ingredient | Amt/unit (mg) |
|---|---|
| Cannabidiol | 60 |
| Naloxone | 10 |
| Anhydrous Dicalcium | 85 |
| Phosphate (Powdered) | 60 |
| Microcrystalline Cellulose | 60 |
| Glyceryl Behenate | 20 |
| Magnesium Stearate | 4 |
| Opadry Red | 20 |
| Purified Water | 110* |

*Remains in product as residual moisture only.

[00462] Examples 28 to 31. 1. Plasticize the Eudragit with Triacetin by mixing. 2. Place the specified Cannabinoid Agonist, Opioid Antagonist, Spray Dried Lactose, and Povidone into a fluid bed granulator and apply the above solution. 3. Pass the granulation through a rotating impeller mill. 4. Dry granulation if moisture content is too high. 5. Melt Stearyl Alcohol and wax

the above granulation by adding melted Stearyl Alcohol onto granulation while mixing. 6. Cool the waxed granulation in a fluid bed dryer. 7. Pass the cooled waxed granulation through a rotating impeller mill. 8. Blend the milled waxed granulation, Talc and Magnesium Stearate. 9. Compress the resultant granulation using a tablet press. 10. Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet.

[00463] EXAMPLE 28

| Ingredient | Amt/unit (mg) |
|---|---|
| Nabilone | 20 |
| Naloxone | 10 |
| Spray Dried Lactose | 60 |
| Povidone | 5 |
| Eudragit RS 30D (dry wt.) | 10 |
| Triacetin | 2 |
| Stearyl Alcohol | 25 |
| Talc | 2.5 |
| Magnesium Stearate | 1.25 |
| Opadry Pink | 6 |
| Purified Water | 34* |

*Remains in product as residual moisture only.

[00464] EXAMPLE 29

| Ingredient | Amt/unit (mg) |
|---|---|
| Dronabinol | 20 |
| Nalmefene | 20 |
| Spray Dried Lactose | 60 |
| Povidone | 5 |
| Eudragit RS 30D (dry wt.) | 10 |
| Triacetin | 2 |
| Stearyl Alcohol | 25 |
| Talc | 2.5 |
| Magnesium Stearate | 1.25 |
| Opadry Pink | 6 |
| Purified Water | 34* |

*Remains in product as residual moisture only.

[00465] EXAMPLE 30

| Ingredient | Amt/unit (mg) |
|---|---|
| Nabilone | 15 |
| Nalmefene | 10 |
| Spray Dried Lactose | 60 |
| Povidone | 5 |
| Eudragit RS 30D (dry wt.) | 10 |
| Triacetin | 2 |
| Stearyl Alcohol | 25 |
| Talc | 2.5 |
| Magnesium Stearate | 1.25 |
| Opadry Pink | 6 |
| Purified Water | 34* |

*Remains in product as residual moisture only.

[00466] EXAMPLE 31

| Ingredient | Amt/unit (mg) |
|---|---|
| THC | 100 |
| Naltrexone | 50 |
| Spray Dried Lactose | 180 |
| Povidone | 15 |
| Eudragit RS 30D (dry wt.) | 30 |
| Triacetin | 6 |
| Stearyl Alcohol | 75 |
| Talc | 7.5 |
| Magnesium Stearate | 4 |
| Opadry Pink | 30 |
| Purified Water | 80* |

*Remains in product as residual moisture only.

[00467] Example 32 to 36. 1. Pass Stearyl Alcohol flakes through an impact mill. 2. Mix specified cannabinoid agonist, opioid antagonist, Eudragit, Ethycellulose and milled Stearyl Alcohol in a twin shell blender. 3. Continuously feed the blended material into a twin screw extruder and collect the resultant strands on a conveyor. 4. Allow the strands to cool on the conveyor. 5. Cut the cooled strands into pellets using a Pelletizer. 6. Screen the pellets and collect desired sieve portion. 7. Fill the extruded pellets into capsules.

[00468] EXAMPLE 32

| Ingredient | Amt/unit (mg) |
|---|---|
| Dronabinol | 15 |
| Naloxone | 10 |
| Eudragit RSPO | 76.5 |
| Ethylcellulose | 4.5 |
| Stearyl Alcohol | 27 |
| | 240 |

[00469] EXAMPLE 33

| Ingredient | Amt/unit (mg) |
|---|---|
| Nabilone | 8 |
| Naloxone | 8 |
| Eudragit RSPO | 76.5 |
| Ethylcellulose | 4.5 |
| Stearyl Alcohol | 27 |

[00470] EXAMPLE 34

| Ingredient | Amt/unit (mg) |
|---|---|
| Cannabidiol | 48 |
| Naltrexone | 25 |
| Eudragit RSPO | 300 |
| Ethylcellulose | 18 |
| Stearyl Alcohol | 108 |

[00471] EXAMPLE 35

| Ingredient | Amt/unit (mg) |
|---|---|
| Cannabidiol | 100 |
| Naltrexone | 20 |
| Eudragit RSPO | 300 |
| Ethylcellulose | 18 |
| Stearyl Alcohol | 108 |

[00472] EXAMPLE 36

| Ingredient | Amt/unit (mg) |
|---|---|
| THC | 100 |
| Naloxone | 20 |
| Eudragit RSPO | 200 |

| | |
|---|---|
| Ethylcellulose | 12 |
| Stearyl Alcohol | 65 |

[00473] EXAMPLE 37

[00474] The cannabinod agonists of any of Examples 1 to 36 is first converted to a solid form and micronized using methods know in the art and then incorporated into the method and process of Examples 1 to 36.

[00475] EXAMPLE 38

One or more cannabinoid agonist is selected from the group consisting of dexanabinol (HU211), BAY 38-7271, Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone, THC (delta-9-tetrahydrocannabinol), nabilone, dronabinol, cannabidiol, cannabinol, cannabichromene, cannabigerol, cannabigerol, anandamide, (R)-methanandamide, 2-arachidonoylglycerol, HU210, desacetyllevonantradol, CP55940, CP55244, URB602, or WIN55212-2, and one or more opioid antagonists selected from the group consisting of naltrexone, methylnaltrexone, nalbuphine, naloxone, nalmefene, cyclazocine, cyclorphan, oxilorphan nalorphine, nalorphine dinicotinate, nalmefene, nadide, levallorphan, N-methylnaltrexone, N-allyllevallorphan, N-methylnaltrexone, alvimopan, N-methylnalmefene and N-allyllevallorphan is prepared according to methods know in the art (e.g., In: Water Insoluble Drug Formulations, Rong Liu (Ed.), Taylor & francis, CRC Press, 2000, Boca raton, FL) and filled as an oil or an emulsion into capsules.

[00476] EXAMPLE 39

[00477] One or more cannabinoid agonist is selected from the group consisting of dexanabinol (HU211), BAY 38-7271, Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone, THC (delta-9-tetrahydrocannabinol), nabilone, dronabinol, cannabidiol, cannabinol, cannabichromene, cannabigerol, cannabigerol, anandamide, (R)-methanandamide, 2-arachidonoylglycerol, HU210, desacetyllevonantradol, CP55940, CP55244, URB602, or WIN55212-2, and one or more opioid antagonists selected from the group consisting of naltrexone, methylnaltrexone, nalbuphine, naloxone,

nalmefene, cyclazocine, cyclorphan, oxilorphan nalorphine, nalorphine dinicotinate, nalmefene, nadide, levallorphan, N-methylnaltrexone, N-allyllevallorphan, N-methylnaltrexone, alvimopan, N-methylnalmefene and N-allyllevallorphan is prepared according to methods know in the art (e.g., In: Water Insoluble Drug Formulations, Rong Liu (Ed.), Taylor & francis, CRC Press, 2000, Boca raton, FL) and compressed into a tablet or filled uncompressed into a capsule.

[00478] EXAMPLE 40

[00479] One or more cannabinoid agonist is selected from the group consisting of dexanabinol (HU211), BAY 38-7271, Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone, THC (delta-9-tetrahydrocannabinol), nabilone, dronabinol, cannabidiol, cannabinol, cannabichromene, cannabigerol, cannabigerol, anandamide, (R)-methanandamide, 2-arachidonoylglycerol, HU210, desacetyllevonantradol, CP55940, CP55244, URB602, or WIN55212-2, and one or more opioid antagonists selected from the group consisting of naltrexone, methylnaltrexone, nalbuphine, naloxone, nalmefene, cyclazocine, cyclorphan, oxilorphan nalorphine, nalorphine dinicotinate, nalmefene, nadide, levallorphan, N-methylnaltrexone, N-allyllevallorphan, N-methylnaltrexone, alvimopan, N-methylnalmefene and N-allyllevallorphan is prepared according to methods know in the art (sse U.S. patent No. 7,229,641, 7,223,770, 7,193,084, 7,186,754, 7,138,113, 7,125,568, 7,112,340, 7,105,685, 7,060,263, 7,037,528, 7,026,290, 6,991,809, 6,977,085, 6,951,656, 6,942,856, 6,923,988, 6,890,549, 6,884,436, 6,869,617, 6,867,024, 6,864,231, 6,835,396, 6,825,179, 6,806,069, 6,790,460, 6,730,330, 6,683,194, 6,683,102, 6,630,161, 6,623,734, 6,589,955, 6,589,562, 6,589,556, 6,569,463, 6,565,873, 6,544,646, 6,541,030, 6,461,634, 6,407,128, 6,406,717, 6,403,116, 6,375,982, 6,348,506, 6,248,363, 6,191,172, 6,045,826, 5,989,583, 5,891,469.

[00480] Various immediate release and controlled release dosage forms comprising releasable or substantially releasable cannabinoid agonist and substantially non-releasable aversive agents selected from the group

comprising cannabinoid antagonists, opioid antagonists and alcohol deterrents may be prepared using the pharmaceutical compositions and methods of the invention.

[00481] The included examples are illustrative but not limiting of the methods and composition of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

[00482] A wide variety of materials can be used for preparing the dosage form according to this invention. This invention therefore contemplates the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

[00483] Other suitable cannabinoid agonist and opioid antagonist dosage forms, as defined in this invention may also be prepared by modification of the examples herein and by use of material other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

[00484] Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

[00485] A wide variety of methods known in the art for the preparation of immediate release and controlled release dosage forms may be incorporated into the invention.

[00486] All of patents and patent applications cited herein are incorporated by reference in their entirety.

[00487] All of publications and references cited herein are incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. An oral dosage form having a reduced potential for abuse, misuse, tampering, toxicity upon tampering and overdose, comprising: (a) a releasable cannabinoid agonist; (b) a releasable or substantially releasable opioid antagonist.
2. An oral dosage form having a reduced potential for abuse, misuse, tampering, toxicity upon tampering and overdose in subjects taking said dosage form as the sole abusable drug, comprising: (a) a releasable cannabinoid agonist; (b) a releasable or substantially releasable opioid antagonist.
3. An oral dosage form having a reduced potential for abuse, misuse, tampering, toxicity upon tampering and overdose in subjects taking said dosage form in the setting of polydrug abuse, comprising: (a) a releasable cannabinoid agonist; (b) a releasable or substantially releasable opioid antagonist.
4. An oral dosage form having a reduced potential for abuse, misuse, tampering, toxicity upon tampering and overdose in subjects taking said dosage form with one or more opioid agonists, comprising: (a) a releasable cannabinoid agonist; (b) a releasable or substantially releasable opioid antagonist.
5. An oral dosage form comprising: (a) a releasable cannabinoid agonist; (b) a releasable or substantially releasable opioid antagonist, said dosage form deterring the abuse, misuse, tampering, toxicity upon tampering and overdose of said cannabinoid agonist.
6. An oral dosage form comprising: (a) a releasable cannabinoid agonist; (b) a releasable or substantially releasable opioid antagonist, said dosage form deterring the abuse, misuse, tampering, toxicity upon tampering and overdose of co-used or co-abused opioid agonist.
7. An oral dosage form comprising any of claim 1 to 6, wherein the abuse, misuse and tampering comprises oral ingestion of the intact

dosage form at dose greater than 2 times, or greater than 4 times, or greater than 10 times, or greater than 20 times maximum recommended dose.

8. An oral sustained release dosage form comprising any of claim 1 to 6, wherein the abuse, misuse and tampering comprises oral ingestion of the tampered (e.g., crushed, ground, solvent extracted) dosage form at the usual prescribed dose, or a tampered dosage form at dose greater than 1.5 times, or greater than 2 times, or greater than 4 times, or greater than 10 times, or greater than 20 times maximum recommended dose.
9. An oral dosage form comprising of any of claim 1 to 6, wherein the abuse, misuse, and tampering comprises non-oral administration of the tampered (e.g., parenteral, intranasal, inhalational use after mechanical, thermal, chemical or solvent extraction) dosage form at the usual prescribed dose, or a tampered dosage form at dose greater than 1.5 times, or greater than 2 times, or greater than 4 times, or greater than 10 times, or greater than 20 times maximum recommended dose.
10. An oral dosage form comprising of any of claim 1 to 6, wherein the abuse, misuse and tampering of the dosage form at least partially blocks the opioid agonist effect when said dosage form is used or abused with opioids.
11. An oral dosage form comprising of any of claim 1 to 6, wherein the abuse, misuse and tampering of the dosage form at least partially blocks the cannabinoid agonist effect.
12. An oral dosage form comprising of any of claim 1 to 6, wherein the abuse, misuse and tampering of the dosage form at least partially blocks the cannabinoid agonist effect and at least partially blocks the opioid agonist effect, when said dosage form is used or abused with opioid agonist.
13. An oral dosage form comprising of any of claim 1 to 6, wherein the abuse, misuse and tampering of the dosage form at partially blocks the

"high", "liking", pleasurable, euphoric, calming, anxiolytic, mood altering, relaxing, psychotomimetic, rewarding or reinforcing effects of the cannabinoid agonist.

14. An oral dosage form comprising of any of claim 1 to 6, wherein the abuse, misuse and tampering of the dosage form at partially blocks the "high", "liking", pleasurable, euphoric, calming, anxiolytic, mood altering, relaxing, psychotomimetic, rewarding or reinforcing effects of the opioid agonist effect, when said dosage form is used or abused with opioid agonists
15. An oral dosage form comprising of any of claim 1 to 6, wherein the abuse, misuse and tampering of the dosage form at partially blocks the "high", "liking", pleasurable, euphoric, calming, anxiolytic, mood altering, relaxing, psychotomimetic, rewarding or reinforcing effects of the cannabinoid agonist and the opioid agonist, when said dosage form is used or abused with opioid agonists.
16. An oral dosage form comprising of any of claim 1 to 6, wherein the dosage form is an immediate release form.
17. An oral dosage form comprising of any of claim 1 to 6, wherein the dosage form is a sustained release form.
18. An oral dosage form comprising of any of claim 1 to 6, wherein the dosage form is both an immediate release and sustained release form.
19. An oral dosage form comprising of any of claim 1 to 6, wherein the dosage form is a tablet form.
20. An oral dosage form comprising of any of claim 1 to 6, wherein the dosage form is a capsule form.
21. An oral dosage form comprising of any of claim 1 to 6, wherein the dosage form is a liquid in a capsule form.
22. An oral dosage form comprising of any of claim 1 to 6, wherein the cannabinoid agonist and optionally, the opioid antagonist are solubilized in an edible oil, fat or wax.

23. A sustained release oral dosage form comprising of any of claim 1 to 6 suitable for twice a day administration, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 47.5% at 1 hour, from about 10% to about 65% at 2 hours, from about 15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours.
24. A sustained release oral dosage form comprising of any of claim 1 to 6 suitable for twice a day administration, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 47.5% at 1 hour, from about 10% to about 65% at 2 hours, from about 15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours.
25. A sustained release oral dosage form comprising of any of claim 1 to 6 suitable for twice a day administration, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 47.5% at 1 hour, from about 10% to about 65% at 2 hours, from about 15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours; said in-vitro release rate being substantially independent of pH in that a difference, at any given time, between an amount of

cannabinoid agonist released at one pH and an amount released at any other pH, when measured in-vitro using the USP Basket or Paddle Method of USP Drug Release test of U.S. Pharmacopeia (2003) at 100 rpm in 900 ml aqueous buffer, is no greater than 30%.

26. A sustained release oral dosage form comprising of any of claim 1 to 6 suitable for once a day administration, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 30% at 1 hour, from about 10% to about 65% at 4 hours, from about 20% to about 70% at 8 hours, from about 25% to about 80% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours.
27. A sustained release oral dosage form comprising of any of claim 1 to 6 suitable for once a day administration, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of from 0% to about 30% at 1 hour, from about 10% to about 65% at 4 hours, from about 20% to about 70% at 8 hours, from about 25% to about 80% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours; said in-vitro release rate being substantially independent of pH in that a difference, at any given time, between an amount of cannabinoid agonist released at one pH and an amount released at any other pH, when measured in-vitro using the USP Basket or Paddle Method of USP Drug Release test of U.S. Pharmacopeia (2003) at 100 rpm in 900 ml aqueous buffer, is no greater than 30%.
28. An oral dosage form comprising of any of claim 1 to 6, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist from 2% to about

50% from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 700 ml of Simulated Gastric Fluid (SGF) at 37 °C.

29. An oral dosage form comprising of any of claim 1 to 6, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist from about 5% to about 45% from the dosage form at one hour when measured by the USP Basket or Paddle Method at 100 rpm in 700 ml of Simulated Gastric Fluid (SGF) at 37 °C.
30. A sustained release oral dosage form comprising of any of claim 1 to 6 suitable for once a day administration, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C between 0% to about 80% at 0.5 hours, and greater than about 40% at 1 hour
31. A sustained release oral dosage form comprising of any of claim 1 to 6, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C between 0% to about 90% at 0.5 hours, and greater than about 60% at 1 hour
32. A sustained release oral dosage form comprising of any of claim 1 to 6, said dosage form providing an in-vitro release rate by weight of cannabinoid agonist and optionally, also the opioid antagonist, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C between 1.6 and 7.2 at 37 °C of between 0% to about 100% at 0.5 hours, and greater than about 60% at 1 hour.
33. The dosage form of claims 1 to 6, where the abuse, misuse, tampering or overdose involves attempts to liberate the cannabinoid agonist from

the dosage form other than by oral ingestion of the intact dosage form as intended by the manufacturer or the prescribing physician.

34. The dosage form of claims 1 to 6, where the abuse, misuse, tampering or overdose involves attempts to liberate the cannabinoid agonist from the dosage form other than by oral ingestion of the intact dosage form at the intended dose.

35. The dosage form of claims 1 to 6, where the abuse, misuse, tampering or overdose involves attempts to liberate the cannabinoid agonist from the dosage form by use of mechanical, thermal and/or chemical means or energy to changes the physical properties of the dosage form.

36. The dosage form of claims 1 to 6, where the abuse, misuse, tampering or overdose involves substantial solvent immersion, solvent extraction, crushing, grinding, dissolution, heating, or combustion of the dosage, followed by systemic administration of the cannabinoid agonist or the dosage form contents by the sublingual, buccal, transmucosal, oral, rectal, parenteral, intranasal, dermal and/or inhalational routes.

37. The dosage form of any of claims 1 to 6, wherein the amount of the cannabinoid agonist in the claimed cannabinoid composition is from about 10 ng to about 1.5 g.

38. The dosage form of any of claims 1 to 6, wherein the amount of the opioid antagonist in the claimed dosage form is from about 10 ng to about 1.5 g.

39. The dosage form of any of claims 1 to 6, further comprising one or more abuse intervention agent(s) in sequestered, partially sequestered, unsequestered, non-releasable, partially releasable or releasable form.

40. The dosage form of claim 39, wherein the abuse intervention agent is sequestered.

41. The dosage form of claims 39, wherein the abuse intervention agent(s) is selected from the group consisting of laxatives, cutaneous vasodilators, headache producing agents, emetics, emetogenic compound, nausea producing compounds, bittering agents, drugs that

cause burning on irritation when in contact with tissue or mucous membranes (e.g., naso-mucosal irritants, oro-mucosal irritants, respiratory irritants), tissue irritants, gastrointestinal irritants, drugs that precipitate withdrawal effects, tissue dyes, lakes and colorants, beverage dyes, lakes and colorants, non-tissue staining beverage dyes, lakes and colorants (i.e, that do not stain or discolor the skin upon ingestion), fecal discolorants, urine discolorants, malodorous agents, opioid antagonists, benzodiazepine antagonists (e.g., flumazenil), and mixtures thereof.

42. The dosage form of any of claims 39 to 41, wherein the abuse intervention agent comprises a non-toxic dye to deter surreptitious attempts at intoxication of another subject.

43. The dosage form of any of claims 39 to 41, wherein the abuse intervention agent comprises a non-toxic bittering agent.

44. The dosage form of any of claims 39 to 41, wherein the abuse intervention agent comprises a non-toxic nasal irritant to deter oral or nasal ingestion of the dosage form.

45. The dosage form of claims 39 to 41, wherein the abuse intervention agent is one or more bittering agents selected from the group comprising T2R or TAS2R receptor agonists, phenylthiourea (phenylthiocarbamide), natural, artificial and synthetic flavor oils, flavoring aromatics, flavoring oils, oleoresins, spearmint oil, peppermint oil, eucalyptus oil, oil of nutmeg, allspice, mace, oil of bitter almonds, menthol, citrus oils including lemon, orange, lime, grapefruit, and fruit essences, sucrose derivatives, sucrose octaacetate, chlorosucrose derivatives, quinine, denatonium, denatonium saccharide and denatonium benzoate.

46. The dosage form of claims 39 to 41, wherein the abuse intervention agent is one or more naso-mucosal, oro-mucosal, respiratory or tissue irritants selected from the group comprising transient receptor potential vanilloid 1 agonists, resiniferanoids, capsaicinoids, phorboid

vanilloids, terpenoid 1,4-unsaturated dialdehydes, capsaicin, capsaicin analogs, resiniferatoxin, olvanil, piperine, zingerone, anandamide, 12- and 15-(S)-hydroperoxy-eicosatetraenoic acids, 5 ¬and 15-(S)-hydroxyeicosatetraenoic acids, phorbol 12-phenylacetate 13-acetate 20-homovanillate, 2 phorbol 12,13-didecanoate 20-homovanillate, leukotriene B(4), tinyatoxin, heptanoylisobutylamide, N-(3-acyloxy-2-benzylpropy1)-N'-dihydroxytetrahydrobenzazepine,
tetrahydroisoquinoline thiourea analogs, heptanoyl guaiacylamide, isobutylamides, guaiacylamides, dihydrocapsaicin, homovanillyl octylester, nonanoyl vanillylamide, formic acid, acetic acid, propionic acidy, butyric acid, valeric acid, caproic acid, caprillic acid, capric acid, oxalic acid, malonic acid, succicnic acid, glu¬taric acid, adipic acid, maleic acid, fumaric acid, citric acid, sodium lauryl sulfate, poloxamer, · sorbitan monoesters, glyceryl monooleates, niacin, mustard, allyl isothiocyaanate and p-hydroxybenzyl isothiocyanate and acetylsalicylic acid.

47. The dosage form of any of claims 39 to 41, wherein the abuse intervention agent is one or more emetogenic or nausea producing agents selected from the group comprising zinc and pharmaceutically acceptable salts thereof, dopamine agonists, apomorphine, ipecac, ipecacuanha, emetine, methylcephaeline, cephaeline, psychotrine, O-methylpsychotrine, ammonium chloride, potassium chloride, magnesium sulfate, ferrous gluconate, ferrous sulfate, aloin, algarot or antimonious oxychloride, antimony trichloride, folate, folic acid, niacin and nicotinamide.

48. The dosage form of any of claims 39 to 41, wherein the abuse intervention agent is one or more cutaneous vasodilators selected from the group comprising niacin, nicotinuric acid, beta-hydroxybutyrate and nicotinic receptor agonists, including agonists at nicotinic receptor HM74A and nicotinic receptor GPR109A.

49. The dosage form of any of claims 39 to 41, wherein the abuse intervention agent is one or more tissue dyes, lakes or colorants, or beverage dyes, lakes or colorants, or a beverage dye, lake and colorant that does not stain or discolor the skin upon ingestion, or a fecal discolorant or a urine discolorant.
50. The dosage form of any of claims 1 to 6, wherein the cannabinoid agonist is selected from the group consisting of dexanabinol (HU211), BAY 38-7271, Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone, THC (delta-9-tetrahydrocannabinol), nabilone, dronabinol, cannabidiol, cannabinol, cannabichromene, cannabigerol, cannabigerol, anandamide, (R)-methanandamide, 2-arachidonoylglycerol, HU210, desacetyllevonantradol, CP55940, CP55244, URB602, or WIN55212-2
51. The dosage form of any of claims 1 to 6, wherein the cannabinoid agonist is selected from the group consisting of 9-THC propyl analog, endocannabinoids, cannabinoid terpenoids, cannabinoid flavonoids, inhibitors of cannabinoid agonist metabolism, inhibitors of monoacylglycerol lipase, cannabidiol propyl analogues, cannabichromene propyl analogues, THC-like ABC tricyclic cannabinoid analogues, synthetic AC bicyclic cannabinoid analogues, synthetic ACD tricyclic cannabinoid analogues, aminoalkylindole compounds or analogs of 2-Arylimino-5,6-dihydro-4H-1,3-thiazines.
52. The dosage form of any of claims 1-6, wherein the cannabinoid agonist is in the form of a pharmaceutically acceptable salt, prodrug, ester, analog, derivative, solvate, complex, polymorph, hydrate, racemate or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof.
53. The dosage form of any of claims 1-6, wherein the cannabinoid agonist is $CB_1$ receptor selective.
54. The dosage form of any of claims 1-6, wherein the cannabinoid agonist is $CB_2$ receptor selective.

55. The dosage form of any of claims 1-5, wherein the cannabinoid agonist has mixed $CB_1$ receptor and $CB_2$ receptor activity.
56. The dosage form of any of claims 1-6, wherein the cannabinoid agonist is a non-$CB_1$ and non-$CB_2$ cannabinoid.
57. The dosage form of any of claims 1-6, wherein the cannabinoid agonist is an anandamide amidase inhibitor.
58. The dosage form of any of claims 1-4, wherein the cannabinoid agonist is an inhibitor of $CB_1$, $CB_2$ or non-$CB_1$/non-$CB_2$ cannabinoid agonist metabolism or reuptake.
59. The dosage form of claim 1 to 6, wherein the opioid antagonist is: (i) μ-opioid receptor selective; (ii) δ-opioid receptor selective; (iii) κ-opioid receptor selective; (iv) an antagonist which possess μ, δ and/or κ-opioid receptor activity and (v) optionally, also has non-opioid receptor pharmacologic activity.
60. The dosage form of claim 87, wherein the opioid antagonist is selected from the group consisting of naltrexone, methylnaltrexone, nalbuphine, naloxone, nalmefene, cyclazocine, cyclorphan, oxilorphan nalorphine, nalorphine dinicotinate, nalmefene, nadide, levallorphan, N-methylnaltrexone, N-allyllevallorphan, N-methylnaltrexone, alvimopan, N-methylnalmefene and N-allyllevallorphan.
61. The dosage form of any of claims 1-6, and 60, wherein the opioid antagonist is in the form of a pharmaceutically acceptable salt, prodrug, ester, analog, derivative, solvate, complex, polymorph, hydrate, racemate or an individual diastereoisomers or enantiomeric isomers thereof or mixture thereof.
62. A method for treating or preventing medical conditions amenable to treatment with cannabinoid agonists comprising administering to a human patient in need thereof an effective amount of the dosage form of any of claims 1-61.
63. A method of claim 62, wherein the medical condition is Alzheimer's disease, schizophrenia, depression, alcoholism, Parkinson's disease,

stroke, premature labor, endotoxic shock, hepatic cirrhosis, atherosclerosis, cancer, glaucoma, emesis, multiple sclerosis, amyotrophic lateral sclerosis, encephalitis, Huntington's disease, obesity, memory impairment, cognitive impairment, hypertension, cardiogenic shock, cerebral ischemia, myocardial infarction, neurotoxicity, febrile seizures and various intestinal disorders.

64. A method for treating or preventing pain, comprising administering to a human patient in need thereof an effective amount of the dosage form of any of claims 1-61

65. The dosage form of claim 1-4, further comprising a non-cannabinoid therapeutically active agent.

66. The dosage form of claim 65 wherein the non-cannabinoid therapeutically active agent is an analgesic.

67. N The dosage form of claim 66, wherein the analgesic is selected from the group comprising NSAIDs, NO-NSAIDs, COX-2 selective inhibitors, acetaminophen, nitroparacetamol, nitric oxide donors, tramadol, beta adrenergic agonists, alpha-2 agonists, selective prostanoid receptor antagonists, opioid receptor agonists, NO-opioid receptor agonists, local anesthetics, purinergic P2 receptor antagonists, NMDA receptor antagonists, gabapentin, pregabalin, gabapentinoids, ligands of alpha(2)delta subunits of voltage-gated calcium channels, neuronal nicotinic receptor agonists, calcium channel antagonists, sodium channel blockers, superoxide dismutase mimetics, p38 MAP kinase inhibitors, TRPV1 agonists, dextromethorphan, dextrorphan, ketamine, glycine receptor antagonists, antidepressants, corticosteroids, and antiepileptics.

68. Kits for use in treating or preventing diseases or disorders amenable to treatment with the dosage form of any of claims 1-67 comprising: (i) a dosage form of the invention; (ii) a container for the dosage form; and optionally, any of (iii) to (vi): (iii) a container for individual units of the dosage form (e.g., individual capsules or tablets, or blister packs);

(iv) educational instructions in any media about any medical condition, its etiology, pathophysiology, consequences and treatment, potential for abuse and diversion and methods for prevention of same and information on the proper use and disposal of the medication; (v) containers or bags for the safe disposal of any remaining unused dosage form, preferably child proof and flushable; and (vi) tamper evident and child proof packaging for the kit and its contents.