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(71) Applicant: **SIMON, David, L.** [US/US]; P.O. Box 618, Mansfield Center, CT 06250-0618 (US).

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(54) Title: IMPROVED OPIOID PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The invention is directed in part to dosage forms comprising a combination of an analgesically effective amount of an opioid agonist analgesic and a neutral receptor binding agent or a partial mu-opioid agonist, the neutral receptor binding agent or partial mu-opioid agonist being included in a ratio to the opioid agonist analgesic to provide a combination product which is analgesically effective when the combination is administered as prescribed, but which is less analgesically effective or less rewarding when administered in excess of prescription. Preferably, the combination product affects an opioid dependent individual differently from an opioid naïve individual, and has a diminished likelihood of being associated with a life-threatening adverse drug reaction, especially in the opioid dependent individual.

IMPROVED OPIOID PHARMACEUTICAL COMPOSITIONS

Related Applications

This application is a PCT International Application for co-pending U.S. Patent Application Serial No. 10/628,089 filed on July 25, 2003, which is a continuation-in-part of co-pending U.S. Patent Application Serial No. 10/306,657 filed November 27, 2002, which is a continuation-in-part applications of U.S. Patent Application No. 09/922,873 filed August 6, 2001, which is now U.S. Patent No. 6,569,866, which is a continuation-in-part of U.S. Patent Application Serial No. 09/152,834 filed September 14, 1998, which is now U.S. Patent No. 6,271,240, which is a continuation-in-part of U.S. Patent Application Serial No. 08/866,334 filed May 30, 1997, now abandoned, which is a continuation-in-part of U.S. Patent Application Serial No. 08/643,775 filed May 6, 1997, also now abandoned.

Background - Field of Invention

The present invention relates to novel pharmaceutical compositions, specifically to those containing an opioid agonist analgesic as at least one component of the composition, and also containing a neutral receptor binding agent of opioid receptors, such as 6-beta-naltrexol and CTAP, as another component of the composition, and a pharmaceutically suitable carrier thereof, and the various methods of use and advantages of such pharmaceutical compositions.

Background – Description of the Prior Art

An opioid agonist analgesic is a drug or pharmaceutical agent that traditionally is used to treat pain, to suppress coughing, to treat diarrhea, and for other medical uses. Depending upon the degree with which a particular opioid agonist medication binds to specific opioid receptor subtypes, such as its affinity for one opioid subtype receptor in preference to another, the opioid agonist analgesic may tend to cause euphoria, or it may tend to cause dysphoria. Some opioid analgesic agonists may also tend to cause nausea by stimulating or inhibiting areas in the brain known as "the vomiting center" and "the chemotactic zone," depending upon the degree with which specific opioid receptor subtypes are activated, and depending to some extent upon the ability of a particular opioid agonist analgesic to penetrate the blood-brain-barrier (BBB). Examples of opioid receptor subtypes are delta-receptors, kappa-receptors, mu-receptors and sigma receptors. These opioid receptor subtypes may be further subcategorized, as for example, mu_1 receptors and mu_2-receptors.

The opioid antagonist nalmefene has unique characteristics that set it apart form other opioid antagonists such as, for example, naloxone and naltrexone. The unique opioid receptor subtype binding profile of nalmefene enables nalmefene alone, as compared to naloxone and naltrexone, to allow preferred antagonism of opioids at the kappa-opioid receptors versus the mu-opioid receptors, which in turn results in an optimal homeostatic balance of dopamine.

Szekely shows a schematic representation of two opposing opioid systems located in the mesolimbic system of the human central nervous system. These systems modulate A10 dopaminergic neurons projecting in the nucleus accumbens. As illustrated in this reference, stimulation of mu-opioid receptors (the mu subtype of opioid receptor) in the ventral tegmental area (VTA), the site of the origin of the A10 neurons, increases dopamine release in

the nucleus accumbens (NA). Selective blockade of this mu-receptor results in significant decrease in dopamine release in the nucleus accumbens. In stark contrast, stimulation of kappa-receptors (the kappa subtype of opioid receptor) in either the VTA or the NA results in a decrease in the amount of dopamine released. Selective blockade of kappa-receptors significantly increases dopamine release.

Spanagel et. al. Demonstrate that tonically active and functionally opposing mu and kappa opioid systems regulate mesolimbic dopamine release in the nucleus accumbens. They report that the injection of mu-opioid agonists such as DAGO into the VTA stimulate mu-opioid receptors and increase the release of dopamine from the VTA into the NA. As would be expected, administration of a mu-opioid receptor antagonist into the VTA decreases dopamine release.

The authors further report that kappa-opioid receptors agonists such as U-6953 infused into the NA inhibit dopamine release there, whereas kappa-opioid receptor antagonists such as nor-BNI increase dopamine release. An "agonist" is a "like" chemical with similar action to a given drug. An "antagonist" is a chemical, often with a similar chemical structure to a given drug, which exerts a dissimilar action to the given drug which exerts a dissimilar action to the given drug, in general preventing the "like" action of that given drug. With opioid receptors, in general, an agonist binds to the receptor and activates it in such a way as to begin a cascade of chemical or pharmacological events so as to result in the end effect related to a particular opioid receptor subtype. In contradistinction, an antagonist will bind to the receptor but not activate it. An antagonist exerts its actions by blocking the receptors from agonists, by physically occupying the space on the receptor where an agonist would otherwise bind.

The opposing mu and kappa opioid systems acting together provide a homeostasis of dopamine levels within the central nervous system. Changes in these opioid systems, such as by activation or blockade of the specific receptors, would therefore be expected to modulate opioid-induced effects that are mediated by mesolimbic pathways. Mu and kappa receptors are found elsewhere in the human body. For example, they have been located in the spinal cord (See Fujimoti, Bakshi, and Behrmann, below) and in other non-central nervous system organs such as the kidney and intestine (See Ohnishi and Kreek, below). Accordingly, the model presented provides a neurochemical framework for understanding the adaptive changes resulting from long term use of opioids, as well as the clinical response elicited by exogenously administered opioid agonists and antagonists having different profiles.

For example, Pan et al report modifications in opioid-induced behavior resulting from changes in these mu and kappa systems. These authors state that the effects of opposing mu and kappa receptors extend to opioid action on emotion, perception and drug reinforcement. While morphine and other mu-opioid agonists increase dopamine release and produce euphoria and place preference, kappa-opioid agonists reduce mesolimbic dopamine release and produce dysphoria and aversion.

Scientists have shown that nalmefene, relative to other opioid antagonists such as naloxone and naltrexone, is significantly more kappa-receptor preferring. By way of example, Kreek et al conclude that nalmefene has more kappa binding activity than either naloxone or naltrexone. Specifically, nalmefene is more potent than either naloxone or naltrexone as a kappa-receptor antagonist, and therefore would block kappa agonists (e.g. The naturally occurring dynorphon) to a greater extent than the other antagonists.

Fujimoto et al. demonstrate differences between mu and kappa receptor effects in the spinal cord. Specifically, these authors report that the administration of dynorphin, a potent kappa agonist, results in decreased analgesia. The dynorphin causes antianalgesic effects at the level of the spinal cord. Fujimoto shows that when a kappa-opioid receptor antagonist such as Cholera Toxin is given, the antianalgesic effect of dynorphin is inhibited.

Bakshi et al. Shows that kappa receptors are widely distributed in the spinal cord, and that administration of dynorphin causes motor impairment. These authors also demonstrate that nalmefene is selective for these intraspinal kappa receptors, and limits dynorphin induced motor dysfunction after spinal cord injury.

Behrmann et al. Report that a single dose of nalmefene has increased activity at kappa receptors and that a single dose of nalmefene exerts a significant neuroprotective effect after acute spinal cord injury, in direct contrast to the mu-preferring opioid antagonist naloxone that showed no significant effect on neurological recovery after spinal cord injury.

Ohnishi et al. Teach the effects on urine production due to kappa-opioid receptor pharmacology at both the level of the pituitary gland and the kidney.

Crain et al. (U.S. Patent No. 5,580,876) teach a method for "selectively enhancing the analgesic potency of a bimodally-acting opioid agonist" which shows that nalmefene much more so that other opioid antagonists, enhances analgesia produced by opioid agonist analgesics. Crain et al. Further teach that much lower concentrations of nalmefene are required to enhance analgesia than with either naloxone or naltrexone, thus further supporting that nalmefene optimized dopamine homeostasis to a much greater extent than other opioid antagonists such as naloxone and naltrexone.

The administration of the opioid antagonists cause upregulation of the opioid receptors present on the surface of cell of the central nervous system. The result of this increased density of opioid receptors is that more opioid receptors will then be available to the naturally occurring endogenous endorphins that are in proximity to these receptors. Because beta-endorphin production is decreased by a mechanism generally known as "negative feedback inhibition" in humans who are chemically dependent upon, and who are still being administered, exogenous opioid agonist analgesics, immediately upon cessation of opioid agonist analgesic administration there is a lack of beta-endorphin the these humans relative to the normal state in humans not chemically dependent upon opioid agonist analgesics. Thus, administration of opioid antagonists not only increase the number of receptors for beta-endorphin to bind to, in addition, these antagonists actually stimulate the production of endorphins by causing the release of negative feedback inhibition of its production. Thus, the cellular changes induced from chronic use of opioid agonist analgesics are reversed to a significant extent. Beta-endorphin attaches to and activates mu-opioid receptors, which results in a cascade of biochemical reactions, the result of which is a increase in central nervous system (CNS) dopamine. These changes brought upon by treatment with an opioid antagonist, such as nalmefene, restore to a human being a more normal physiological state, which will decrease the human's cravings for, and reduce the human's tolerance to, exogenously administered opioid agonist analgesics.

This upregulating effect of opioid antagonists in humans for treating addiction to opioid agonist analgesics has not been appreciated by those skilled in the art, particularly in the case of nalmefene, which provides distinct pharmacological and clinical advantages over other opioid antagonist for treating addiction to opioid agonist analgesics. Nalmefene tends to

optimize CNS dopamine by virtue of its greater affinity for kappa-oppioid receptors relative to mu-opioid receptors, and compared to naltrexone and other opioid antagonists.

A sufficiently high concentration of opioid antagonist must be present at the opioid receptor blocked, e.g. at a mu_1-opioid receptor, to prevent an exogenously administered opioid agonist analgesic or its metabolite from binding to the receptor, but not such a high concentration as to totally block binding of endogenous beta-endorphin to that receptor. Again, nalmefene is the unique opioid antagonist that will block beta-endorphin at mu_1-opioid receptors to a relatively lesser extent that other antagonists such as naloxone and naltrexone, while at the same time having optimal blocking of kappa-opioid receptors by endogenous molecules such as dynorphins. Therefore, nalmefene alone, as compared to naloxone and naltrexone, not only optimizes dopamine regulation during detoxification, but also following detoxification. Thus, nalmefene is not an analogous compound to other opioid antagonits because nalmefene provides distinct pharmacological and clinical advantages for post detoxification treatment of patients addicted to opioid narcotics not available with other opioid antagonists.

DEFINITIONS:

"Opioid antagonist" not qualified by the words "neutral" or "preferred, for the treatment of addictions" = "inverse opioid agonist" = "inverse agonist" is a compound, molecule or peptide that binds to an opioid receptor causing a tendency toward activation or excitation of the opioid receptor, meaning an increase in the signaling from the receptor to endogenous cellular systems upon which the signals from the opioid receptor act, *e.g.*

resulting in an increase in intracellular cAMP, and shall include the base, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and mixtures thereof.

"Neutral opioid antagonist" = "neutral receptor binding agent" = "neutral antagonist" is a compound, molecule or peptide that binds to an opioid receptor without causing a tendency toward activation or inactivation of the opioid receptor different from the state of activity that the opioid receptor is in at the time of binding to it by the neutral receptor binding agent, meaning that signaling from the opioid receptor to endogenous cellular systems upon which the signals from the opioid receptor act are not effectively increased or decreased, *e.g.*, intracellular cAMP is relatively unchanged, and shall include the base, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and mixtures thereof.

"CTAP" is the neutral receptor binding agent D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2, a cyclic, penicillamine-containing octapeptide.

"Preferred opioid antagonist for the treatment of addictions" is an opioid binding agent that is not an inverse opioid agonist at mu_1 opioid receptors in individuals that are dependent or addicted to any opioid agonist analgesic.

"Opioid agonist" = "opioid agonist analgesic" is a compound, molecule or peptide that binds to an opioid receptor causing a tendency toward inactivation of the opioid receptor, meaning an decrease in the signaling from the receptor to endogenous cellular systems upon which the signals from the opioid receptor act, *e.g.*, resulting in a decrease in intracellular cAMP. The term "opioid agonist" shall include the base of the opioid, pharmaceutically acceptable salts thereof, stereoisomers thereof, ethers and esters thereof, and mixtures thereof.

"Efficacy" relates to the degree of signaling from the receptor to endogenous cellular systems upon which the signals from the opioid receptor act. For example, high efficacy

would mean, *e.g.*, that upon binding to the receptor by an agonist compound, molecule or peptide, a high degree of inhibition of adenyl cyclase occurs in association with relatively lower intracellular concentration(s) of cAMP. Likewise, low efficacy would mean, *e.g.*, that upon binding to the receptor by the agonist compound, molecule or peptide, adenyl cyclase inhibition is of a relatively low degree in association with relatively less of a decrease in intracellular concentration(s) of cAMP. There may be a spectrum of efficacies among different compounds that bind to opioid receptors.

"Potency" is the affinity to which the compound, molecule or peptide binds to the receptor. Sometimes, the reciprocal of affinity is expressed as a dissociation constant (K_D). A given compound, molecule or peptide may have a high potency and a high efficacy, or a high potency and a low efficacy, or a low potency and a high efficacy or a low potency and a low efficacy, or various graduations of efficacy and potency.

"Partial mu-opioid agonist" is a compound, molecule or peptide that has an efficacy lower than a "full" mu-opioid agonist. The terms "opioid agonist" and "partial" opioid agonist are often quoted in the literature as terms relative to one another. For example, morphine is often cited simply as a mu-opioid agonist, and compared to it, buprenorphine is a partial mu-opioid agonist because of its lower efficacy. Generally, buprenorphine is thought to have a higher potency and a lower efficacy compared to morphine.

"Intrinsic mu-receptor activity" is the amount of signaling from the receptor to endogenous cellular systems upon which the signals from the opioid receptor act, that result when the mu-receptor is not acted upon by an opioid agonist, partial mu-opioid agonist or an opioid antagonist. It is theoretically thought of as the amount of signaling of an unbound or

"empty" receptor that is not conformationally altered from its natural resting state under a given set of environmental or historical circumstances.

"Any licit use" of an opioid preparation means to use an opioid for a prescribed or otherwise legitimate and legal medical reason, such reasons including but not limited to the medical treatment of cough, loose stool or diarrhea (including as associated with irritable bowel syndrome), shivering, dependency or addiction, heart disease and pain (including as associated with fibromyalgia, cancer, arthritis, traumatic injury, neuralgia, somatic pain, visceral pain, neuropathic pain, etc.).

The term "parenterally" as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

The term "effective analgesia" is defined for purposes of the present invention as a satisfactory reduction in or elimination of pain, along with a tolerable level of side effects, as determined by the human patient.

The term "sustained release" is defined for purposes of the present invention as the release of the drug (opioid analgesic) from the oral formulation at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective analgesic concentration or "MEAC") but below toxic levels over a period of time indicative of a twice-a-day or a once-a-day formulation.

The term "steady state" refers to a time when the rate of elimination of a drug is the same as the rate of absorption of that drug into the body.

To put the above-described definitions in a context that better explains them, consider the research article "Activity of opioid ligands in cells expressing cloned mu opioid receptors" by Gharagozlou, *et al.* in *BMC Pharmacology 2003, 3:1.* In this work, efficacies and

potencies of various mu-opioid acting compounds were determined relative to the naturally occurring beta-endorphin and the common opioid agonist analgesic morphine, by determining how much cAMP was released (expressed in terms of IC50), and by assigning an affinity constant (K_i) a given compound, respectively. For further clarification, 6-beta-naltrexol is a neutral receptor binding agent and nalbuphine is a partial mu-opioid agonist under applicable environmental and historical conditions.

For completeness sake, it should be understood that activation of mu and delta opioid receptors open potassium channels, which decreases calcium conductance. The activation of kappa opioid receptors also reduces calcium channels, but by the mechanism of directly closing the calcium channels. Calcium conductance can be measured by recording an action potential resulting from movement of calcium ions. Excitation or inhibition of the calcium current is sometimes represented by a change in action potential duration.

Gekker, Lokensgard and Peterson in *Drug and Alcohol Dependence 64 (2001), pages 257-263* describe in "Naltrexone potentiates ant-HIV1 activity of antiretroviral drugs in CD4+ lymphocyte cultures" how naltrexone acts to increase the anti-HIV effects of drugs used to treat HIV infection and AIDS. Li, Wang, Tian *et al.* in *Journal of Infectious Disease, Jan1;185(1):118-22* teach in "Methadone enhances human immunodeficiency virus infection of human immune cells" that the opioid agonist methadone increase HIV virus activation and replication. These authors reiterate their findings in the *Journal of Infectious Disease 2002 Jan1;185(1):118-22* in another article with the same title. Mahayni and Minor wrote a letter in the *American Journal of Hospital Pharmacy Nov;48(11):2480-1* stating that "research data suggests that the narcotic antagonists naltrexone and naloxone may possess anti-HIV activity," but they make no mention of nalmefene or neutral receptor binding agents. Dr.

Bernard Bihari wrote a letter in *AIDS Patient Care 1995 Feb;9(1):3* observing that trials of low-dose naltrexone with AIDS patients showed that the naltrexone was associated with significant and advantageous differences in the incidence of opportunistic infections, and that AIDS patients administered naltrexone maintained "good" CD4 lymphocytes. He intimates that this may be due to the immunological role of endorphins as "key hormones" in regulating the immune system. Schluger, Ho, Borg *et al.* in *Alcohol Clinical Experimental Research 1998 Oct;22(7):1430-6* in their article "Nalmefene causes greater hypothalamic-pituitary-adrenal activation than naloxone in normal volunteers: implications for treatment of alcoholism" demonstrate that "kappa- and delta- opioids may play important roles in the regulation of the hypothalamic-pituitary-adrenal axis." (They do not discuss any possible role related to HIV). Suzuki, Chuang, Chuang *et al.* in *Advances in Experimental Medicine and Biology 2001;493:81-7* in a chapter titled "Morphine upregulates kappa-opioid receptors of human lymphocytes" teach that "chronic morphine use also induces immunomodulatory and immunosuppressive effects, as especially evident in HIV-infected patients," and that this phenomenon involves kappa-opioid receptors.

This, taken together with the advantageous opioid receptor subtype binding profile of nalmefene as described herein and which was noted prior to October 1998 in U.S. Patent Application Serial No. 08/643,775 filed May 6, 1996 supports the present invention that teaches nalmefene as a preferential treatment and prophylactic medication for HIV viral infection and AIDS. The present invention also teaches the manufacture and use of a pharmaceutical preparation for preventing HIV infection as a prophylactic measure and for treating HIV infection in HIV-infected individuals and those with AIDS.

The present invention also teaches the superiority of nalmefene for treatment of alcoholism compared to other opioid antagonists due to a decreased tendency for cardiac dysrhythmias in alcoholic patients at increased risk for such dysrhythmias that was not previously appreciated by those skilled in the art. Nalmefene has been used to treat alcoholism, most notable by Dr. Barbara Mason in Florida. However, it has really been used in the prior art as an analogous compound to naltrexone, which the invention at hand clearly demonstrates it is not. In addition to the distinguishing characteristics of nalmefene demonstrated previously herein, as it relates to a drug addiction when the drug abused is ethanol ("alcohol") the following advantages of nalmefene are encompassed in the present invention. Smetnev, Gorgaaslidze, Zinkin *et al.* in "*Terk Arkh 1988;60(1):49-51*" [orginial article in Russian], point out that more than 29% of alcoholic patients have cardiac abnormalities manifesting as "arrhythmical paroxysms." Faintuch in "*Rev Hosp Clin Fac Med Sao Paulo 1995 Jan-Feb;50(1):76-9*" [original article in Portuguese] states that "both acute and chronic alcohol consumption precipitate arrhythmias." Fabrizio and Regan in "*C rdiovasc Drugs Ther 1994 Feb;8(1):89-94* report in their article "Alcoholic cardiomyopathy" that "atrial arrhythmias have been shown to occur during the early ethanol withdrawal phase in patients without other clinical evidence of heart disease." It is common knowledge in medical practice that "holiday heart syndrome" consists of cardiac dysrhythmia due to the high ingestion of ethanol around the time of holiday celebrations, which quite unfortunately is sometimes fatal. Actions of alcohol inducing dysrhythmias on a cellular level have been described in animal models. For instance, Nakamura, Houchi, Ohe an Namba in *Alcohol Clinical Experimental Research 1999 Apr;23(4 Suppl):81S-84S* teach in their article "Increase in beating rate of cultured chick cardiac myocytes by ethanol and inhibition of the

increase by antiarrhythmic drugs" that "drinking alcohol sometimes causes cardiac arrhythmia." Going back to 1976, Ettinger *et al.* teach in the *American Heart Journal 1976 Jan;91(1):66-*78 in their article "Cardiac conduction abnormalities produced by chronic alcoholism" that "cardiac conduction abnormalities and rhythm disturbances are common clinical findings" in alcoholic patients with manifestations of long-term alcohol consumption. Those skilled in the art of treating alcoholic human patients clinically have failed to appreciate what is demonstrated by Caldwell, Nagarajan, Chryssanthis and Tuttle in *Pharmacology 1990;41(3):161-6* in their articled titled "Actions of the opioid antagonist, nalmefene, and congeners on reperfusion cardiac arrhythmias and regional left coronary blood flow." Caldwell *et al.* reach that nalmefene "reduced the incidence of reperfusion arrhythmias significantly when compared to the saline control," and that "neither N-methyl-nalmefene . . . nor (+)nalmefene . . provided any protection against reperfusion arrhythmias." They concluded that nalmefene prevents the occurrence of such arrythmias. These studies, taken within the context of treating human alcoholics with opioid antagonists, support the present invention that nalmefene, as distinguished from other opioid antagonists used in treatment of drug addiction (*e.g.* naltrexone), is a preferred drug in the treatment of alcoholic patients. This, not being obvious to others skilled in the art, has not been attributed to nalmefene in the context of clinical trials using nalmefene to treat alcoholism. The present invention teaches that nalmefene, being non-analogous to naltrexone, is a preferred drug for the treatment of alcoholism. Schluger *et al* (*ibid*) do not make the case for nalmefene as being a preferred drug for treatment in alcoholism. In fact, they state merely "the effects of nalmefene and also naltrexone on modulating the tonic inhibition exerted by endogenous opioids acting at kappa- and delta-, as well as mu-, opioid receptors on the hypothalamic-pituitary-adrenal ("HPA")

axis may be related to their [emphasis added] established efficacy as treatment agents for alcoholism (see page 1434, *Ibid*). Further, with regard to nalmefene being a non-analogous preferred agent to naltrexone for alcoholism, Schluger *et al.* only conclude "nalmefene, as well as other kappa and perhaps delta-opioid antagonists and agonists, may therefore be useful tools to further elucidate some of the basic physiology and pathophysiology of the HPA axis, the endogenous opioid system, the biology of addictions, and the intersections between them" (see page 1435, *Ibid*). Such vague and convoluted language does not teach nalmefene as a preferred opioid antagonist to treat alcoholism, therefore the present invention is not obvious to one of ordinary skill in the art because of Schluger *et al.*

The present invention also teaches that 6-beta-naltrexol and CTAP are preferred opioid antagonists for the treatment of addictions, most notably opioid addiction, as is nalbuphine. Wang, Raehal, Blisky and Sadee in their article "Inverse agonists and neutral antagonists at mu opioid receptor (MOR): possible role of basal receptor signaling in narcotic dependence" in the *Journal of Neurochemistry 2001 Jun;77(6):1590-600*, teach that the neutral opioid antagonist 6-beta-naltrexol possesses certain important advantages over other opioid antagonists in that 6-beta-naltrexol does not inhibit intrinsic mu-opioid receptor "agonist-like activity" to the degree that the opioid antagonists naltrexone, naloxone and nalmefene do. This is important in a previously opioid-dependent patient recently detoxified and withdrawn from opioids to which a sustained release opioid antagonist is administered. Clinical evidence indicates that naltrexone pellets implanted into humans as part of a detoxification procedure is associated with substantial withdrawal related signs and symptoms in the post-detoxification period. Accordingly, 6-beta-naltrexol or CTAP would not cause the

same degree of opioid withdrawal related symptoms in the post detoxification period if it were administered in lieu of naltrexone.

The present author has previously quite unexpectedly discovered that nalbuphine, also known by the trade name Nubain® (Endo Pharmaceuticals, Chadds Ford, PA), reverses detrimental effects of fentanyl such as respiratory depression without totally inhibiting mu-opioid agonist-like activity. The present author has also quite surprising discovered that nalbuphine, although precipitating opioid withdrawal in actively opioid-dependent patients due to antagonist effects, also relieves opioid withdrawal symptoms in patients in the immediate post-detoxification period. Thus, by incorporating nalbuphine hydrochloride in a putty-like semi-sol described herein for administration and sustained delivery of the water-soluble nalbuphine molecule, a method of blocking opioid receptors from "pure" opioid agonist analgesics, such as morphine, heroin or fentanyl is manifested, while simultaneously allowing for some mu-opioid agonist-like activity. Thus, the present invention recognizes nalbuphine as a partial mu-opioid agonist, which may be interpreted that it is also a partial mu-opioid antagonist, and at the very least allows for intrinsic mu-opioid receptor activity.

Opioid agonist analgesics have long been a cornerstone of pharmaceutical management of pain and other medical maladies such as cough, loose stool or diarrhea. However, use of opioid agonist analgesics may be accompanied by feeling euphoria as a reaction apart from relief of pain, or may be accompanied by other pharmaceutical effects as to create a wanting of the opioid agonist analgesic as an issue separate and distinct from the issue of pain relief. It is undesirable for a human patient to want to be administered an opioid agonist analgesic for reasons other than relief of pain or prescribed treatment of licit medical maladies such as loose stool. Such a wanting could result in the opioid agonist analgesic

being administered in quantities greater than that required to treat pain and other licit medical maladies, which would result in waste of opioid agonist analgesic, and an increase in spending for opioid agonist analgesics. This is of great societal significance in managing the allocation of scarce resources available in the treating health care system in general. Any wastage of money on a pharmaceutical or medication results in less money available for other needed resources, be they other medications or health care services. In and of itself, a decrease in wanting of opioids apart from pain relief and other licit uses (hereafter "any licit use") would be of great of great utility, whether it be in an opioid naïve individual (*i.e.*, one that has not been previously exposed to opioid analgesics) or an individually chronically exposed to opioid agonist analgesics (*e.g.*, a chronic pain patient, as one who is long suffering from malignant or cancer-related pain).

There have been attempts to reduce the effective amount of opioid agonist analgesic for any licit use. Such attempts have included the co-administration of opioids with NMDA-receptor antagonists or relatively low doses of opioid antagonist. These methods, if effective, could theoretically serve the desired purpose of reducing wastage of opioids, however these methods have not been demonstrated to decrease the wanting of the opioid apart from any licit use, and in fact, could theoretically potentiate the opioid agonist effect to possibly increase the wanting desire of the opioid agonist analgesic, which would have the opposite of the desired effect to decrease wastage and optimize management of scare health care resources.

Mayer, *et al* teach that NMDA (N-methyl-D-aspartate) receptor antagonists such as dextromethorphan or dextrophan may be combined with opioid agonist analgesics for the prevention of opioid tolerance (U.S. Patent No. 5,654,281). However, this may make the opioid agonist effectively more potent, and Mayer does not teach that this invention will

decrease the wanting or desire for being administered opioids apart from the effect of any licit use.

Caruso teaches that NMDA receptor antagonists administered with narcotic agonist/antagonists increase the analgesic effect of the agonist/antagonist (U.S. Patent 6,007,841). Again, this may render the opioid agonist more potent and does not speak to decreasing the wanting of the opioid apart from the effect of any licit use. Caruso makes no mention of neutral receptor binding agents.

Crain *et al* teach that very small doses of opioid antagonists (inverse opioid agonists) may potentiate the analgesic effect of opioid agonist analgesics (U.S. Patent Nos. 5,580,876 and 5,767,125). Crain does not teach decreasing the wanting desire of opioid analgesics apart from any licit use, nor decreasing the tendency for illicit use. In fact, the technology taught by Crain *et al*, because it teaches potentiation of opioid analgesic effects by combining the analgesic with an inverse opioid agonist, may actually increase the tendency for illicit self-administration by a physically dependent human subject in direct contradistinction to the present invention. Crain does not teach the use of neutral receptor binding agents.

The present author teaches that a pharmaceutical composition comprising nalmefene and an opioid agonist analgesic may optimize dopamine homeostasis while dissuading a human from abusing the opioid agonist analgesic (U.S. Patent No. 6,103,258, hereafter "'258"). '258, however, does not utilize the advantages of neutral receptor binding agents as does the present invention.

Palermo, *et al* (U.S. Patent No. 6,228,863) and Kaiko, *et al* (U.S. Patent No. 6,277,384) teaching compositions for oral administration containing opioid agonist analgesics and opioid antagonists in varying amounts depending upon the particular opioid agonist and

antagonist used. These formulations, however, have the potential to produce severe precipitated abstinence syndrome in susceptible individuals, unlike the present invention. Unintentional precipitated abstinence syndrome ("withdrawal"), especially when severe, can have serious deleterious effects on humans, such as precipitation of catecholamine release, exaggerated stress response and myocardial ischemia. Unmonitored, as may occur with an unintentional withdrawal, this could be life threatening.

Smith, *et al* teach that a kappa-2 opioid receptor agonist may be combined with a mu opioid receptor agonist such that relatively low sub-therapeutic doses of each may result in therapeutic analgesia (U.S. Patent No. 6,310,072). However, Smith does not teach that this invention reduces the likelihood that the drug combination will be less likely to be administered in doses greater than prescribed as does the present invention..

Kaiko and Colucci (U.S. Patent No. 6,475,494 or "'494") teach the combination of an opioid agonist analgesic and an inverse opioid agonist. They do not teach or claim the combination of an opioid agonist analgesic and a neutral receptor binding agent as in the present invention. The invention of '494 teaches an aversive reaction in physically dependent human subjects that the present invention modifies so as not to be so inhumane or dangerous to such physically dependent human subjects. Another important advantage of the present invention over '494 is that '494 includes the inverse opioid agonist naltrexone, which is metabolized in humans to 6-beta-naltrexol. Thus, with '494 the inverse opioid agonist naltrexone competes for binding to mu-opioid receptors with the neutral receptor binding agent 6-beta-naltrexol, complicating the predictability of the intended effect of the naltrexone, and reducing if not eliminating the beneficial effect of the 6-beta-naltrexol that may be present as a metabolite, as compared to naltrexone. '494 does not teach, contemplate or even

hint at administering a neutral receptor binding agent or a partial mu-opioid agonist of the requisite efficacy and potency with an opioid agonist analgesic as described herein.

U.S. Patent Application No. 20010049375 of Sadee, *et al.* teach the administration of a neutral receptor binding agent solely as a method for the treatment of drug dependency. Sadee, *et al.* do not teach toward a method or pharmaceutical composition containing an opioid agonist analgesic and a neutral receptor binding agent at all, let alone as a means to administer an opioid agonist analgesic for any licit use to non-dependent humans with the objective(s) of the present invention.

Summary of the Invention

The present invention provides a structural composition comprising a therapeutic dose of opioid agonist analgesic in combination with an amount of a neutral receptor binding agent such as 6-beta-naltrexol or CTAP, or in combination with nalbuphine, effective to allow for the positive effects of the opioid agonist analgesic, while at the same time exerting relatively less antagonistic effects at mu-opioid receptors compared to other opioid antagonists, when the opioid agonist analgesic is administered in recommended therapeutic doses, such that the agonist actions of the opioid agonist analgesic will far outweigh any antagonism by 6-beta naltrexol, CTAP or nalbuphine at said mu-opioid receptors. If excessive amounts of the structural composition comprising 6-beta naltrexol, CTAP or nalbuphine and opioid agonist analgesic are administered, enough 6-beta naltrexol, CTAP or nalbuphine shall be administered as to begin to antagonize or block mu-opioid receptors from the exogenously administered opioid agonist analgesic, while simultaneously allowing for some intrinsic mu-opioid agonist-like activity. Thus, excessive opioid agonist analgesic is blocked, preventing

overdose or excessive euphoric effects, while the likelihood of triggering a withdrawal response is greatly diminished.

The present invention provides for a pharmaceutical composition comprising an opioid agonist, a neutral receptor binding agent or a partial mu-opioid agonist, in a pharmaceutically acceptable carrier thereof. This is of great societal importance because the invention tends to limit opioid effects to those intended or prescribed for any licit use while further improving upon previous technology by i) providing for a means of differentiating effects of an analgesic composition in opioid dependent versus non-dependent individuals, and ii) decreasing the likelihood of precipitating adverse physical effects that could be of a serious or life-threatening nature as an unintended side effect of the pharmaceutical composition.

As discussed above, neutral receptor binding agents, such as 6-beta-naltrexol and CTAP, in stark distinction from traditional opioid antagonists such as nalmefene, naloxone and naltrexone, have unique binding characteristics at opioid-receptors, most notably mu-receptors. These unique binding profiles of neutral receptor binding agents allow for preferred blocking at mu-receptors, such that dopamine release in the central nervous system ("CNS") will tend to be less inhibited due to actions at mu-receptors than would be the case with equivalent blocking a mu-receptors by traditional opioid antagonists such as nalmefene, naloxone or naltrexone.

As taught by BJ Morris and MJ Millan (*British Journal of Pharmacology* 1991 Apr;102(4):883-6), neutral receptor binding agents do not have the same ability to cause up-regulation of opioid receptors as inverse opioid agonists do. This is of paramount importance in distinguishing neutral receptor binding agents as unique, non-analogous to inverse opioid

agonists, and greatly preferred in the context of the present invention. This was not appreciated by Crain, Kaiko or the like. Upregulation of mu-opioid receptors following naltrexone administration, for example, renders an individual much more sensitive to opioid agonist effects, greatly increasing the likelihood of unintentional opioid agonist overdose. Such would not be the case (to the same degree at least) with neutral receptor binding agents such as 6-beta-naltrexol or CTAP.

Objectives of the Invention

It is an object of the invention to provide an oral or parenteral dosage form of an opioid analgesic which is subject to less abuse potential via the oral route than prior commercially available dosage forms that is more humanely administered with less likelihood of a serious or life-threatening adverse event compared to technology in the prior art.

It is a further object of the present invention to provide an oral or parenteral dosage form of an opioid analgesic and method which provides therapeutic analgesia and which also provides a limit on the agonist effects of the opioid analgesic such that a human subject would not be motivated to take much more, *e.g.* about 2-3 times more than the prescribed dose, of opioid analgesic for any licit use.

It is a further object of the present invention to provide an oral or parenteral dosage form of an opioid analgesic that in non-dependent or opioid naive individuals will not result in any appreciable withdrawal effect and will still allow effective analgesia in opioid naïve individuals even when administered at much more than the prescribed dose, while tending to negate excessive opioid agonist effects when administered at much more than the prescribed dose in opioid-dependent or opioid addicted individuals.

It is a further object of the present invention to provide an oral or parenteral dosage form of an opioid analgesic and a method for providing therapeutic analgesia in a manner which is not as positively reinforcing in opioid naive individuals or humans that are not opioid-dependent taking much more than the prescribed dose, e.g., at least about 2-3 times the prescribed dose of the opioid, as compared to the same amount of opioid without the neutral receptor binding agent or partial mu-opioid agonist.

It is a further object of the invention to provide a method of treating pain in human patients with an oral or parenteral dosage form of an opioid analgesic while reducing the abuse potential of dosage form.

It is a further object of the invention to provide a method of manufacturing an oral dosage form of an opioid analgesic such that it has less oral abuse potential.

Detailed Description of the Invention

The present invention combines an opioid analgesic with a compound, molecule or peptide that also binds an opioid receptor such that the compound, molecule or peptide will compete with the opioid analgesic for a binding site on the opioid receptor, where the compound, molecule or peptide has relatively low or negligible efficacy in comparison to the opioid analgesic, but which at a minimum will allow for the opioid receptor's intrinsic mu-receptor activity when bound to it.

An opioid receptor is acted upon by a compound, molecule or peptide (hereafter, "molecule") in such a way that the molecule causes a change in physical conformation of the receptor such that the conformational change induces a concomitant change in an opioid receptor-linked protein (*e.g.*, a "G-protein") that is associated with induction of further

chemical changes such as phosphorylation involving a protein or enzyme, or activation/inactivation of an enzyme such as adenyl cyclase, which further induces other chemical changes such as increase or reduction of "second messengers" such as adenosine-3':5'-cyclic phosphate or "cAMP" (from interaction of adenosine monophosphate or "AMP" and ATP, *e.g.*). The molecule may bind the receptor with a relatively high affinity and a relatively high efficacy, such as the prototypical mu-opioid agonist analgesic. Alternatively, an opioid receptor may be left in absence of binding molecules, such that the second messengers are produced in reliance upon the intrinsic mu-receptor activity.

The conformational status of the receptor or the coupling of the opioid receptor-linked protein or the number of receptors available on the cell membrane, may be a function of the past history of exposure to opioid agonists and/or opioid antagonists (see Yoburn, *et al.* in *Pharmacology Biochemistry and Behavior, Vol. 51, Nos. 2/3, pp. 535-539, 1995* and Paronis and Holtzman in *Journal of Pharmacology and Experimental Therapeutics, Vol. 259, No. 2, pp. 582-9, 1991* and Liu and Prather in *Molecular Pharmacology, Vol. 60, No. 1, pp. 53-62, 2001*). Thus, intrinsic mu-receptor activity of an opioid receptor may be expected to differ depending upon whether the receptor is found in an opioid naïve individual, an opioid dependent or addicted individual, or an individual that is prescribed opioid antagonists (inverse opioid agonists).

An opioid dependent human may have a violent aversive reaction consistent with the phenomenon of acute withdrawal when subjected to an opioid antagonist (inverse opioid agonist), whereas an opioid naïve human may have no such reaction at all when subjected to the same amount and dosage of the inverse opioid agonist. The opioid dependent human just written about may experience much less an aversive reaction when administered a neutral

receptor binding agent of equivalent potency to the opioid antagonist described in this paragraph, such a difference having great clinical significance. Acute opioid withdrawal of the kind being discussed is expected to increase firing of neurons in the locus coeruleus of the brain and be associated with clinically significant rises in catecholamines such as epinephrine, norepinephrine and dopamine. This surge in catecholamines increases the work load of the heart, and in a patient with compromised cardiovascular function can result in myocardial ischemia, irregular conduction of electrical currents throughout the heart, and other maladies that can cause great physical peril to the human experiencing such medical signs. Drug addicts are at increased risk for cardiac pathology involving conduction disturbances and blood supply to the heart, as well as valvular heart disease that can further complicate an aversive withdrawal reaction. Therefore, it is undesirable to administer a drug dosage form that is likely to, or intended to, cause such an aversive reaction in a human population expected to be administered opioid agonist analgesics.

As described by Wang, *et al. (Journal of Neurochemistry, Vol. 77, No. 6, pp. 1590-1600, 2001)* naltrexone is an inverse opioid agonist in animals pretreated with morphine. This model would indicate that humans physically dependent on opioid analgesics would respond to naltrexone as an inverse opioid agonist. However, 6-beta-naltrexol in animals acts as a neutral receptor binding agent irrespective of morphine pretreatment. It follows then that 6-beta-naltexol would be a neutral receptor binding agent in humans dependent on or addicted to opioid analgesics.

Combinations of opioid agonist analgesics and the neutral receptor binding agent 6-beta-naltrexol which are orally administered in ratios which are equivalent to the ratio of, e.g., 6-beta-naltrexol to hydrocodone set forth herein are considered to be within the scope of the

present invention. Equipotent doses of other neutral receptor binding agents such as 6-alpha-naltrexol, 6-alpha-naloxol, 6-beta-naloxol and 6-beta-naltrexamine in clinically equivalent ratios as set forth herein are also within the scope of the present invention.

It is known that when co-administered with morphine, heroin or other opioids on a chronic basis, naltrexone blocks the development of physical dependence to opioids. It is believed that the method by which naltrexone blocks the effects of heroin is by competitively binding at the opioid receptors. 6-alpha- and 6-beta-naltrexol and -naloxol, and 6beta-naltrexamine would therefore be expected to also prevent or reduce the development of tolerance, but with the previously mentioned great advantages of neutral receptor binding agents. For example, in formulations of the present invention in which the opioid is hydrocodone bitartrate 15 mg, the amount of 6-beta-naltrexol included in the formulation is from about 0.5 mg to about 12 mg, and preferably from about 0.75 mg to about 8 mg 6-beta-naltrexol per 15 mg hydrocodone.

The ratio described herein is based on the following calculations from Kaiko and Colucci ('494), and extrapolating from data from Rukstalis, *et al. (Alcoholism Clinical and Experimental Research, Vol. 24, No. 10, pp. 1593-96, Oct. 2000)* in which 2.6 times the dose of naltrexone was used for 6-beta-naltrexol in treating Wistar rats:

Equianalgesic Doses of Opioids

Opioid	Calculated Dose (mg)
Oxycodone	13.5
Codeine	90.0
Hydrocodone	15.0
Hydromorphone	3.375
Levorphanol	1.8
Meperidine	135.0
Methadone	9.0
Morphine	27.0

Based on a preferred ratio of 6-beta-naltexol per 15 mg of hydrocodone, the approximate ratio of 6-beta-naltrexol to 1 mg of each opioid is set forth below:

Weight Ratio of 6-beta-naltrexone per Dose Opioid

Opioid Agonist	Weight Ratio 6-beta-naltrexol per 1 mg Opioid Agonist
Oxycodone	0.020 to 0.770 of 6-beta-naltrexol
Codeine	0.003 to 0.114 " "
Hydrocodone	0.018 to 0.694 " "
Hydromorphone	0.089 to 3.082 " "
Levorphanol	0.164 to 5.777 " "
Meperidine	0.002 to 0.077 " "
Methadone	0.031 to 1.154 " "
Morphine	0.010 to 0.385 " "

Of course, there may be differences in both efficacy and potency of 6-beta-naltrexol among the Wistar rats and humans, and a more definitive ratio of neutral binding agent to opioid analgesic should ideally be calculated. However, in light of the present invention, one skilled in the art would be able to do so in routine laboratory trials prior to large scale clinical testing as is typically carried out in the United States pharmaceutical industry. In fact, Kaiko and Colucci lay the foundation for such routine testing in '494. For example, The amount of neutral binding agent which is useful to achieve an optimal ratio of opioid agonist to neutral receptor binding agent may be determined at least in part, for example, through the use of "surrogate" tests, such as a VAS scale (where the subject grades his/her perception of the effect of the dosage form) and/or via a measurement such as pupil size (measured by pupillometry). Other commonly employed instruments in the industry are the Addiction Research Center Inventory ("ARCI") and the POMS rating scale. In addiction, a technique such as applying a low amp electrical current transcutaneously to a subject and recording the amperage at various stages of discomfort is a way to determine or simulate effective

analgesia. These techniques are well described in the literature and are well known to one skilled in the art.

Such measurements allow one skilled in the art to determine the dose of neutral receptor binding agent relative to the dose of opioid agonist analgesic that causes a diminution in the opioid effects of the agonist. Subsequently, one skilled in the art can determine the level of neutral receptor binding agent that causes a reduction in the slope of the dose-response curve for the opioid as well as the level of neutral receptor binding agent that minimizes "liking scores" or opioid reinforcing properties in human subjects.

Other factors in extrapolating dosages of 6-beta-naltrexol from dosages of naltrexone are the relative biological and elimination half-lives of the respective drugs, the volumes of distribution of the respective drugs, and the bioavailability according to the route of administration, *i.e.*, "is the bioavailabilty of one drug similar or different from that of the other drug?" However, these techniques are industry standards and are well known to one skilled in the art, hence in light of the present invention the optimal ratio of neutral receptor binding agent to opioid agonist analgesic is readily obtained. Incorporated herein by way of reference are Ferrari, *et al.* "Serum time course of naltrexone and 6-beta-naltrexol levels during long-term treatment in drug addicts," *(Drug and Alcohol Dependence, Vol. 52, No. 3, pp. 211-220, 1998)*, and Porter, *et al.*, "In vivo and in vitro potency studies of 6-beta-naltrexol, the major human metabolite of naltrexone," *(Addiction Biology, Vol. 7, No. 2, pp. 219-225, April 2002)*.

Opioid analgesics which are useful in the present invention include all opioid agonist analgesics that have a greater efficacy than the particular neutral receptor binding agent or partial mu-opioid agonist of the invention, including but not limited to alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol,

clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, noroxycodone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, pro-poxyphene, sufentanil, tilidine, tramadol, mixtures of any of the foregoing, salts of any of the foregoing, and the like.

In certain preferred embodiments, the opioid agonist analgesic is selected from the group consisting of hydrocodone, morphine, hydromorphone, oxycodone, codeine, levorphanol, meperidine, methadone, or salts thereof, or mixtures thereof. In certain preferred embodiments, the opioid agonist is hydrocodone. Equianalgesic doses of these opioids, in comparision to a 15 mg dose of hydrocodone, are set forth herein (above).

Although hydrocodone is effective in the management of pain, there has been an increase in its abuse by individuals who are psychologically dependent on opioids or who misuse opioids for illicit reasons. Previous experience with other opioids has demonstrated a decreased abuse potential when opioids are administered in combination with a narcotic antagonist especially in patients who are ex-addicts. Weinhold L L, *et al.* "Buprenorphine Alone and in Combination with Naltrexone in Non-Dependent Humans" *(Drug and Alcohol Dependence 1992; 30:263-274)*; Mendelson J., *et. al.*, "Buprenorphine and Naloxone

Interactions in Opiate-Dependent Volunteers," *(Clin Pharm Ther 1996; 60:105-114);* both of which are hereby incorporated by reference.

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple central nervous system and gastrointestinal actions. Chemically, hydrocodone is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-one, and is also known as dihydrocodeinone. Like other opioids, hydrocodone may be habit forming and may produce drug dependence of the morphine type. In excess doses hydrocodone, like other opium derivatives, will depress respiration.

Oral hydrocodone is also available in Europe (Belgium, Germany, Greece, Italy, Luxembourg, Norway and Switzerland) as an antitussive agent. A parenteral formulation is also available in Germany as an antitussive agent. For use as an analgesic, hydrocodone bitartrate is commercially available in the United States only as a fixed combination with non-opiate drugs (i.e., acetaminophen, aspirin, ibuprofen, etc.) for relief of moderate or moderately severe pain. Administration of available hydrocodone preparations in excess of prescribed dosing can therefore lead to ingested of supra-therapeutic doses of acetaminophen or NSAID, possibly leading to toxic physical reactions such liver toxicity or gastrointestinal hemorrhage. Therefore, it would be of great utility to decrease the tendency toward excessive administration or ingestion of available hydrocodone pharmaceuticals.

A common dosage form of hydrocodone is in combination with acetaminophen, and is commercially available, e.g., as Lortab® in the U.S. from UCB Pharma, Inc. as 2.5/500 mg, 5/500 mg, 7.5/500 mg and 10/500 mg hydrocodone/acetaminophen tablets. Tablets are also available in the ratio of 7.5 mg hydrocodone bitartrate and 650 mg acetaminophen; and 7.5 mg hydrocodone bitartrate and 750 mg acetaminophen. Hydrocodone in combination with

aspirin is given in an oral dosage form to adults generally in 1-2 tablets every 4-6 hours as needed to alleviate pain. The tablet form is 5mg hydrocodone bitartrate and 224 mg aspirin with 32 mg caffeine; or 5 mg hydrocodone bitartrate and 500 mg aspirin. A relatively new formulation comprises hydrocodone bitartrate and ibuprofen. Vicoprofen®, commercially available in the U.S. from Knoll Laboratories, is a tablet containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen. The present invention is contemplated to encompass all such formulations, with the inclusion of any orally active neutral receptor binding agents or partial-mu opioid agonists with potency and efficacy profiles within the inventive parameters set forth herein.

The abuse potential of opioid analgesics such as hydrocodone is curtailed by the inventive combinations of the present invention. More particularly, it has been discovered that it is possible to combine in a single oral dosage form an opioid analgesic together with a small amount of neutral receptor binding agent or partial mu-opioid agonist, to achieve a product which still provides analgesia but which diminishes the likelihood that a human subject will abuse the drug by taking more than one tablet at a time, *e.g.*, 2-3 times more than the usually prescribed dose.

The combination of opioid agonist analgesic and neutral receptor binding agent or partial mu-opioid agonist can be employed in admixtures with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for oral administration, known to the art. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and

diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like. They can also be combined where desired with other active agents, e.g., other analgesic agents. For oral administration, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gelcaps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients which are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

Aqueous suspensions contain the above-identified combination of drugs and that mixture has one or more excipients suitable as suspending agents, for example pharmaceutically acceptable synthetic gums such as hydroxypropylmethylcellulose or natural gums. Oily suspensions may be formulated by suspending the above-identified combination of drugs in a vegetable oil or mineral oil. The oily suspensions may contain a thickening agent such as beeswax or cetyl alcohol. A syrup, elixir, or the like can be used wherein a sweetened vehicle is employed. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

The method of treatment and pharmaceutical formulations of the present invention may further include one or more drugs in addition to the opioid analgesic and neutral receptor binding agent or partial mu-opioid agonist, which additional drug(s) may or may not act synergistically therewith. Thus, in certain embodiments, a combination of two opioid analgesics may be included in the formulation, in addition to a neutral receptor binding agent. For example, the, dosage form may include two opioid analgesics having different properties, such as half-life, solubility, potency, and a combination of any of the foregoing. In yet further embodiments, one or more opioid analgesics is included and a further non-opioid drug is also included, in addition to the neutral receptor binding agent or partial mu-opioid agoinist. Such non-opioid drugs would preferably provide additional analgesia, and include, for example, aspirin; acetaminophen; non-sterioidal antiinflammatory drugs ("NSAIDS"), e.g., ibuprofen, ketoprofen, etc.; N-methyl-D-aspartate (NMDA) receptor antagonists, e.g., a morphinan such as dextromethorphan or dextrorphan, or ketamine or d-methadone; cycooxygenase-II inhibitors ("COX-II inhibitors"); glycine receptor antagonists; and/or alpha3-beta4 nicotinic receptor antagonists.

In certain preferred embodiments of the present invention, the invention allows for the use of lower doses of the opioid analgesic by virtue of the inclusion of an additional non-opioid agonist, such as an NSAID or a COX-2 inhibitor. By using lower amounts of either or both drugs, the side effects associated with effective pain management in humans are reduced.

Suitable non-steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin,

zomepirac, tiopinac, zido-metacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Useful dosages of these drugs are well known to those skilled in the art.

N-methyl-D-aspartate (NMDA) receptor antagonists are well known in the art, and encompass, for example, morphinans such as dextromethorphan or dextrorphan, ketamine, d-methadone or pharmaceutically acceptable salts thereof. For purposes of the present invention, the term "NMDA antagonist" is also deemed to encompass drugs that block a major intracellular consequence of NMDA-receptor activation, e.g. a ganglioside such as GM_1 or GT_{1b} a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(6-aminothexyl)-5-chloro-1-naphthalenesulfonamide. These drugs are stated to inhibit the development of tolerance to and/or dependence on addictive drugs, e.g., narcotic analgesics such as morphine, codeine, etc. in U.S. Pat. Nos. 5,321,012 and 5,556,838 (both to Mayer, et.al.), and to treat chronic pain in U.S. Pat. No. 5,502,058 (Mayer, et. al.), all of which are hereby incorporated by reference. The NMDA antagonist may be included alone, or in combination with a local anesthetic such as lidocaine, as described in these Mayer, *et al.* patents.

The treatment of chronic pain via the use of glycine receptor antagonists and the identification of such drugs is described in U.S. Pat. No. 5,514,680 (Weber, et al.), hereby incorporated by reference.

COX-2 inhibitors have been reported in the art and many chemical structures are known to produce inhibition of cyclooxygenase-2. COX-2 inhibitors are described, for example, in U.S. Pat. Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213;

5,475,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311, all of which are hereby incorporated by reference. Certain preferred COX-2 inhibitors include celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), MK-966, nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof Dosage levels of COX-2 inhibitor on the order of from about 0.005 mg to about 140 mg per kilogram of body weight per day are therapeutically effective in combination with an opioid analgesic. Alternatively, about 0.25 mg to about 7 g per patient per day of a COX-2 inhibitor is administered in combination with an opioid analgesic.

In yet further embodiments, a non-opioid drug can be included which provides a desired effect other than analgesia, e.g., anti-tussive, expectorant, decongestant, antihistamine drugs, local anesthetics, and the like.

In another preferred embodiment, a nicotinic receptor antagonist can be included, most preferably an alpha-3-beta-4-nicotinic receptor antagonist as described by the present inventor in U.S. Patent Application No. 10/127,358 which is hereby incorporated by reference.

An oral dosage form according to the invention may be provided as, for example, granules, spheroids, beads, pellets (hereinafter collectively referred to as "multiparticulates"). An amount of the multiparticulates which is effective to provide the desired dose of opioid over time may be placed in a capsule or may be incorporated in any other suitable oral solid form. Alternatively, the oral dosage form may be in the form of a tablet.

Controlled Release Dosage Forms

The opioid agonist/neutral receptor binding agent combination can 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 that is incorporated into a matrix along with the opioid agonist and opioid antagonist, or may be applied as a sustained release coating.

In embodiments in which the opioid analgesic comprises hydrocodone, the sustained release oral dosage forms may include analgesic doses from about 8 mg to about 50 mg of hydrocodone per dosage unit. In sustained release oral dosage forms where hydromorphone is the therapeutically active opioid, it is included in an amount from about 2 mg to about 64 mg hydromorphone hydrochloride. In another embodiment, the opioid analgesic comprises morphine, and the sustained release oral dosage forms of the present invention include from about 2.5 mg to about 800 mg morphine, by weight. In yet another embodiment, the opioid analgesic comprises oxycodone and the sustained release oral dosage forms include from about 2.5 mg to about 800 mg oxycodone. The opioid analgesic may comprise tramadol and the sustained release oral dosage forms may include from about 25 mg to 800 mg tramadol per dosage unit. The dosage form may contain more than one opioid analgesic to provide a substantially equivalent therapeutic effect. Alternatively, the dosage form may contain molar equivalent amounts of other salts of the opioids useful in the present invention.

In one preferred embodiment of the present invention, the sustained release dosage form comprises such particles containing or comprising the active ingredient, 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.

The particles are preferably film coated with a material that permits release of the opioid agonist/neutral receptor binding agent combination 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, inert, and tack-free.

In certain embodiments, the particles comprise normal release matrixes containing the opioid analgesic with the neutral receptor binding agent or partial mu-opioid agonist.

Coatings

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of 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 opioid 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 eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions that 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.

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), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic (with or without the COX-2 inhibitor) 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. Coatings derived from aqueous dispersions--are described, e.g., in detail in U.S. Pat. Nos. 5,273,760 and 5,286,493, hereby incorporated by reference.

Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include those described in U.S. Pat. Nos. 5,324,351; 5,356,467, and 5,472,712.

Alkycellulose Polymers

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.

One commercially available aqueous dispersion of ethylcellulose is Aquacoat® (FMC

Corp., Philadelphia, Pa., U.S.A.). 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.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). 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

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 co-polymers.

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.

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.

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 Eudragite® from Rohm Tech, Inc. 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.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragie® 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.

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:Eudragit® 90% 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

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, 30 however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

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.

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.

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

When a hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

The controlled release bead formulations of the present invention slowly release the therapeutically active agent, 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.

Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent 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 opioid to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., Opadry® commercially available from Colorcon, Inc.) 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 hydroxypropylmethylcellulose. 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. 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 ethyl-cellulose, 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.

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.

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.

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.

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 hydroxypropylmethylcellulose.

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

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 hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

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. 3,845,770; 3,916,889; 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 Bead Formulations

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 may also utilize a controlled release matrix that affords in-vitro dissolution rates of the opioid within the preferred ranges and that releases the opioid 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. For example, a matrix in addition to the opioid analgesic and (optionally) COX-2 may include:

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 active agent and which melts (or softens to the extent necessary to be extruded) may be used in accordance with the present invention.

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. Of these polymers, acrylic polymers, especially Eudragit® RSPO--the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25 degrees and 90 degrees 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.

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

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 allylamine 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.

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 300 to about 200 degrees C., preferably from about 45 degrees to about 90 degrees 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 carnauba 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 degrees to about 100 degrees C.

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 degrees and 90 degrees Celsius 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.

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.

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 opioid 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 acetyl alcohol or acetostearyl 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 opioid 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 mass) of the total dosage.

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 opioid 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.

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.

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.

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

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

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 opioid or an opioid 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 hydroxyalkyl cellulose/opioid 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 opioid.

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 (Trade Mark, FMC Corporation). 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 co-polymer, 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

Sustained release matrices can also be prepared via melt-granulation or melt-extrusion techniques. 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 intended in the present invention are found in U.S. Pat. No. 4,861,598.

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).

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. 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.

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

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the opioid analgesic, 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 multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 to about 24 hours.

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; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

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.

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.

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.

In another preferred embodiment, a suitable amount of the multiparticulate extrudate is 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, (Arthur Osol, editor), 1553-1593 (1980), incorporated by reference herein.

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681 (Klimesch, et. al.), described in additional detail above.

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 opioid analgesic compound utilized and the desired release rate, among other things.

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 therapeutically active agent for prompt therapeutic effect. The immediate release therapeutically active agent 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.

The sustained release formulations of the present invention preferably slowly release the therapeutically active agent, 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.

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the therapeutically active agent, which is added thereafter to the extrudate. Such formulations typically will have the therapeutically active agent blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. 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 DESCRIPTION OF PREFERRED EMBODIMENTS:

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

A direct comparison of the competitive opioid receptor binding properties of 6-beta-naltrexol or other neutral receptor binding agents following its co-administration with various

opioid agonists has not been undertaken previous to the present invention, to the knowledge of the inventor. However, such run-up dosing regimens are easily implemented by those skilled in the art in light of the present invention.

The scope of the invention is not intended to be limited by the ratios of neutral receptor binding agent to opioid agonist analgesic within a pharmaceutical composition recited herein because optimal such ratios can only be determined by experimentation that in light of the present invention is routine, typical and expected of such an invention, and which is readily carried out by one skilled in the art. Further, in the experiments carried out by Kaiko and Colucci in '494, the interactions of naltrexone with 6-beta-naltrexol *in vivo* are not predicted by their work in that the serum half-life of 6-beta-naltrexol is longer than the time period used to evaluate area under the curve (AUC) in relation to naltrexone (see figues 11, *e.g.*, which record AUC at 6 hours for varying doses of naltrexone). Further, it is difficult to extrapolate the effect of a plasma concentration of 6-beta-naltrexol alone when compared to a plasma containing concentrations of both naltrexone and 6-beta-naltrexone. For instance, how much of the competitive binding of opioid receptors, irrespective of efficacy or effect on receptor intrinsic activity, is due to the naltrexone or due to 6-beta-naltrexol? This question can be answered, however, as taught herein, by examining the various effects (data points as previously described) associated with given concentrations of naltrexone and the metabolite 6-beta-naltrexol, respectively (which are both easily measured, and which *were* measured by Kaiko and Colucci, though not directly addressed in '494), and the same various effects associated with the same given concentration(s) of 6-beta-naltrexol (in absence of naltrexone), and then by subtracting out the 6-beta-naltrexol effects from both samples. One can then estimate the effects due to naltrexone alone and 6-beta-naltrexol alone. Kaiko and Colucci

make no mention of such efforts. Of course, that those skilled in the art as Kaiko and Colucci are, have not described combining a neutral receptor binding agent with an opioid agonist analgesic, despite all the work in this general area done by such skilled artisans, speaks strongly to the fact the present invention is neither obvious, nor taught by the prior art. It is clear that there is utility of the present invention, and it is still further apparent that the present invention has a great commercial marketplace. That Sadee and Wang also have not taught or contemplated the present invention is further evidence of its non-obviousness.

'494 also doesn't take into consideration dosing over a given time period. It addresses taking a larger amount than prescribed (2-3 times the prescribed amount) of an opioid analgesic preparation as a single bolus, but doesn't address, *e.g.*, taking the prescribed dose more often than prescribed, or taking the prescribed or excessive dose over a period of several days. This is important because the half-life of hydrocodone is approximately 3.8 hours, while that of naltrexone is approximately 4 hours, and that of 6-beta-naltrexol 13 hours (*Physicians' Desk Reference, 54th ed., 2000*). Though the half-life of hydrocodone matches up fairly well with naltrexone, over time 6-beta-naltrexol will tend to accumulate relative to hydrocodone (when administered together), such that maximum steady-state effects of 6-beta-naltrexol will not be seen for several days. This is the case whether 6-beta-naltrexol is administered in the absence or presence of naltrexone. Kaiko and Colucci appear to address only steady state effects relating to hydrocodone and naltrexone, ignoring the component effect inherent in the present invention, *i.e.*, the effect of "just" 6-beta-naltrexol. This is not a trivial matter, because 6-beta-naltrexol concentrations arising secondarily from metabolism of the parent naltrexone may vary greatly and are not predictable enough for a consistent effect of a pharmaceutical composition (see, for examples, "Serum time course of naltrexone and 6beta-naltrexol levels

during long term treatment in drug addicts" by Ferrari, *et al.* in *Drug and Alcohol Dependence, Vol. 52, pp. 211-220, 1998*, and "Kinetics and inhibition of the formation of 6beta-naltrexol from naltrexone in human liver cytosol" by Porter, *et al.* in *British Journal of Clinical Pharmacology, Vol. 50, pp. 465-472, 2000*). Further, Kaiko and Colucci do not distinguish "aversive effects" among and between opioid naïve humans and opioid dependent humans. Thus, it appears that Kaiko and Colucci in no way anticipate the present invention.

The present invention is also not intended to be limited by theoretical mechanism, but rather to comprise the spirit and scope of the specifications herein including its claims and any subsequent allowed claims.

Example 1:

A recommended therapeutic dose of morphine, e.g. 0.15 mg/kg morphine, preferably in the form of morphine sulfate, is co-administered parenterally with 0.00025 to 0.0015 milligrams per kilogram (mg/kg) 6-beta naltrexol, preferably in the form of 6-beta naltrexol hydrochloride, more preferably 0.0007 mg/kg 6-beta naltrexol. For a young adult 70 kg human, for example, 10.5 mg morphine sulfate is administered parenterally, along with 0.049 mg, or 49 micrograms (ug), 6-beta naltrexol hydrochloride parenterally. This small amount of 6-beta naltrexol, consistent with the present invention, produces minimal appreciable effect at mu-opioid receptors in relation to the 10.5 mg dose of morphine.

In a preferred embodiment of the present invention, morphine sulfate and 6-beta naltrexol hydrochloride are co-existent in a common medium compatible for parenteral administration in the ratio, of 0.15 mg active morphine to 0.0007 mg active 6-beta naltrexol. Ideally, if administered subcutaneously, the total amounts of the two co-administered active

drugs would be contained within an injectable volume of approximately 1 to 2 milliliters (cc) or less for a 70 kg adult human.

Example 2:

Among the most commonly written prescriptions in the United States, are the prescriptions for combination oral analgesics consisting of an opioid agonist analgesic and a non-opioid analgesic such as acetaminophen, aspirin, ibuprofen or other non-steroidal anti-inflammatory drug ("NSAID"). By way of example only, the combination of oxycodone and acetaminophen, commonly known by the brand name Percocet®, is very often prescribed for a wide variety of pain syndromes, including pain secondary to surgery or trauma, and malignancies. Similarly, the drug formulation commonly known by the brand name Percodan® is composed of oxycodone and aspirin, and the opioid agonist analgesic hydrocodone in its bitartrate form is combined with the non-opioid analgesic acetaminophen.

Orally administered combination drugs consisting of an opioid agonist analgesic and another drug(s) or medication(s) are among the most widely abused opioid agonists abused. If these combination drugs contain acetaminophen, as in the case with Percocet®, a large amount of Percocet® tablets may be orally ingested, so much so as to cause a toxic load of acetaminophen to be delivered. Acetaminophen is widely known to be toxic to the liver of humans when administered in excessive dosages, or when abused by self-administration either intentionally or unintentionally. Often, because of the tolerance built up to the opioid agonist analgesic component of the Percocet®, the patient will progressively ingest more and more Percocet® tablets over time in an attempt to satisfy the effect of the opioid agonist analgesic at mu opioid receptors. Because of the stealth adverse effects of acetaminophen toxicity, often a human may not be aware of harm caused to him or her by the large ingestion

of acetaminophen in the combination drug formulation, until a medical exam reveals abnormal liver function, or until liver failure suddenly becomes apparent. Compounding this problem is the fact that orally administered drugs are delivered relatively directly to the liver, by a mechanism commonly called "first pass metabolism." Thus, there is presently a great need to formulate an orally administrable combination drug therapy that would allow for the additive or synergistic effects of combining analgesics, such as opioids and acetaminophen, but that could prevent or strongly limit the likelihood of developing liver failure secondary to liver toxicity.

In the case of Percodan®, a large amount of Percodan® tablets may be orally ingested, so much so as to cause a toxic load of aspirin to be delivered. Aspirin and other NSAIDs are widely known to cause gastrointestinal bleeding of humans when administered in excessive dosages. Often, because of the tolerance built up to the opioid agonist analgesic component of the Percodan®, the patient will progressively ingest more and more Percodan® tablets over time in an attempt to satisfy the effect of the opioid agonist analgesic at mu opioid receptors. Because of the unobvious early signs of adverse effects of aspirin or NSAID toxicity, often a human may not be aware of harm caused to him or her by the large ingestion of aspirin or NSAID in the combination drug formulation, until a medical exam reveals abnormal gastric function, or until an acute gastric hemorrhage suddenly becomes apparent. Compounding this problem is that when aspirin or other NSAIDs are administered orally, or *per os*, they are delivered directly to the stomach through the esophagus where their breakdown begins to occur in direct contact with the gastric mucosa lining the stomach. This is the very site of the caused gastric bleeding. Thus, there is presently a great need to formulate a orally administrable combination drug therapy that would allow for the additive or synergistic

effects of combining analgesics, such as opioids and NSAIDs (of which aspirin is an example), but that could prevent or strongly limit the likelihood of developing gastrointestinal bleeding.

Hydrocodone (as hydrocodone bitartrate, for example) and other opioid agonist analgesics are commonly mixed with other non-opioid analgesic drugs in formulating combination medications.

By way of example only, if a combination medication tablet that is formulated with 10 milligrams (mg) of hydrocodone and 0.2 mg nalbuphine (=200 micrograms) is ingested orally, only about 30 microgram (mcg) of nalbuphine will be delivered unmetabolized to the bloodstream. A formulation proportionate to 10 mg hydrocodone and 100 mcg nalbuphine (0.1 mg), perhaps mixed with acetaminophen 500 mg, would be expected to produce analgesia not significantly or very appreciably different from a formulation of 10 mg hydrocodone and 500 mg acetaminophen without nalbuphine. However, if a human were to ingest two such formulated tablets every four hours, as commonly occurs when human patients self-administer these medications in larger than doses prescribed or intended by a physician, then over a 12-plus hour period a human would ingest 8 tablets comprising 80 mg hydrocodone and 0.8 mg nalbuphine. Because the plasma half-life of both hydrocodone and acetaminophen is approximately 3 hours, and the plasma elimination half-life of nalbuphine is approximately 3.5 hours, nalbuphine will tend to accumulate over time relative to hydrocodone and acetaminophen such that as more time progressively transpires the nalbuphine serum concentration relative to hydrocodone serum concentration will increase as the tablets are ingested over that time. Further, by administering the medication every 4 hours, steady state concentration of nalbuphine will occur in approximately 24 hours. Eventually,

this will cause an appreciably different effect of the opioid agonist analgesic. This effect could include prevention of mortal respiratory depression, or lack of satisfaction due to opioid ingestion. The exact nature of this interaction is easily altered by one skilled in the art by changing the relative amounts of nalbuphine to opioid agonist analgesic in the tablet, as well as by altering the pharmacokinetic profile of either drug by including a sustained release preparation of either the nalbuphine or the opioid agonist analgesic. This would be calculated during the normal course of experimentation routine for deriving such data. Such experimentation is routinely employed in formulating pharmaceutical preparations to required standards. The dosages are thus described generally in terms of pharmacological effect.

Though hydrocodone and oxycodone are mentioned by way of example here, the scope of the invention encompasses any orally administered opioid agonist analgesic. Such applicable opioid agonist analgesics include the following opioids and their derived salts and bases: morphine, propoxyphene, fentanyl, methadone, levomethadyl (LAAM) and codeine.

Example 3:

Ideally, 6-beta-naltrexone is administered in such a fashion such that steady state concentration of it is reached in about four and a half half-lives, or in about two and a half days. Thus, the goal is to have a steady state concentration of 6-beta-naltrexol at two and a half days that is below threshold for competing with co-administered opioid agonist analgesic (*e.g.*, hydrocodone, oxycodone) to any clinically significant extent which by that time has also reached its own steady-state concentration. Therefore, one must determine at what concentration in a given individual (an opioid naïve human, or an opioid-dependent human) 6-beta-naltrexol will not noticably adversely alter effective analgesia due to the opioid agonist analgesic. Ideally, this threshold is one that is overcome by taking either more than the

prescribed dose of analgesic after two and a half days or taking the analgesic more often than prescribed after two and a half days. That concentration of 6-beta-naltrexol (or other neutral receptor binding agent) may or may not be independent of the concomitant serum concentration of opioid agonist analgesic. Whether or not it is independent depends upon the relative potencies, or affinities for the mu-opioid receptor, of the 6-beta-naltrexol and opioid agonist. We know that in the opioid dependent model, the efficacy of 6-beta-naltrexol is a net zero, neither increasing or decreasing the intrinsic activity of the opioid receptor, and that in all cases the efficacy of the opioid agonist analgesic is significant. Therefore, the determining factor for whether or not the sub-threshold steady-state concentration of 6-beta-naltrexol is dependent upon the concentration of the opioid agonist is the relative potencies of the neutral receptor binding agent (*e.g.*, 6-beta-naltrexol) and the opioid agonist analgesic (*e.g.*, hydrocodone, oxycodone). Potencies of various opioid analgesics are known to those skilled in the art insofar as much some practitioners of the art hold such information as trade secrets. *In* vivo and *in* vitro potencies of 6-beta-naltrexol are described by Porter *et al.* in "In vivo and in vitro potency studies of 6beta-naltrexol, the major human metabolite of naltrexone," (*Addiction Biology, Vol. 7, No. 2, pp. 219-25, April 2002* – the abstract of which is incorporated by way of reference). The ideal situation is when the relative potencies allow for a sub-threshold steady-state concentration of neutral receptor binding agent that tends to be independent of the opioid agonist analgesic concentration. In such cases, then a dose of 6-beta-naltrexol can be calculated from experimentation, in light of the present invention, that is constant ("D_{6BN}"). D_{6BN} is then formulated with differing doses of opioid analgesic such as to create a "library" of pharmaceutical compositions, each comprising a specific dose of opioid agonist analgesic, D_{6BN}, and a pharmaceutical carrier thereof. For example, oxycodone is

commercially available from several U.S. pharmaceutical concerns in a number of dosage forms of varying dose, *e.g.*, 10 mg, 20 mg, 40 mg and 80 mg (from Purdue Pharma, LLP, Stamford, Connecticut). The present invention then, teaches various pharmaceutical compositions containing, *e.g.*, 10 mg oxycodone and $D_{6BN\text{-}oxy}$, 20 mg oxycodone and $D_{6BN\text{-}oxy}$, 40 mg oxycodone and $D_{6BN\text{-}oxy}$, and 80 my oxycodone and $D_{6BN\text{-}oxy}$, depending upon, of course, the relative potency of 6-beta-naltrexol to oxycodone. Alternatively, the present invention teaches in a like manner, various pharmaceutical compositions containing, *e.g.*, 5 mg hydrocodone and $D_{6BN\text{-}hyd}$,7.5 mg hydrocodone and $D_{6BN\text{-}hyd}$, and 10 mg hydrocodone and $D_{6BN\text{-}hyd}$ (where "$D_{6BN\text{-}oxy}$" is the dose of 6-beta-naltrexol resulting in steady-state blood concentration of 6-beta-naltrexol that is immediately sub-threshold to diminishing effective analgesia of therapeutic doses of oxycodone, and "$D_{6BN\text{-}hyd}$" is the dose of 6-beta-naltrexol resulting in steady-state blood concentration of 6-beta-naltrexol that is immediately sub-threshold to diminishing effective analgesia of therapeutic doses of hydrocodone).

This is accomplished in the following way.

An easily comparable number of groups of humans, *e.g.*, A,B,C . . N, matching in general demographic characteristics (*e.g.*, sex, age, etc.), of sufficient number to yield meaningful results, are grouped as follows:

Group A: Opioid naïve humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 0.5 mg of 6-beta-naltrexol every 6 hours

Group B: Opioid naïve humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 1.0 mg of 6-beta-naltrexol every 6 hours

Group C: Opioid naïve humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 2.0 mg of 6-beta-naltrexol every 6 hours

Group D: Opioid naïve humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 4.0 mg of 6-beta-naltrexol every 6 hours

Group E: Opioid naïve humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 8.0 mg of 6-beta-naltrexol every 6 hours

Group F: Opioid naïve humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 16 mg of 6-beta-naltrexol every 6 hours

Group G: Opioid dependent humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 0.5 mg of 6-beta-naltrexol every 6 hours

Group H: Opioid dependent humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 1.0 mg of 6-beta-naltrexol every 6 hours

Group I: Opioid dependent humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 2.0 mg of 6-beta-naltrexol every 6 hours

Group J: Opioid dependent humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 4.0 mg of 6-beta-naltrexol every 6 hours

Group K: Opioid dependent humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 8.0 mg of 6-beta-naltrexol every 6 hours

Group L: Opioid dependent humans receiving 15 mg hydrocodone and a hypothetical dose of 6-beta-naltrexol, $D_{6BN\text{-}hyd}$, *e.g.*, 16 mg of 6-beta-naltrexol every 6 hours

Group M: Opioid naïve humans receiving 15 mg hydrocodone and no 6-beta-naltrexol every six hours

Group N: Opioid dependent humans receiving 15 mg hydrocodone and no 6-beta-naltrexol every 6 hours

Each group is tested over approximately three days or more, measuring the following parameters at reasonable intervals (*e.g.*, every 6 hours): i) serum hydrocodone concentration, ii) serum 6-beta-naltrexol concentration, iii) ARCI scores, iv) POMS scores, v) visual analog scores ("VAS") as described by Kaiko and Colucci, vi) pupil size as in routine pupilometry or as described by Kaiko and Colucci, vii) the electrical current presented to the skin that is associated with a particular score on a scale measuring discomfort due to administration of the electrical current to the skin of the human subject, viii) scales measuring discomfort due to administration of the electrical current to the skin of the human subject. A ninth parameter that may be measured is electroencephalographic ("EEG") activity from the scalp of the human subject. A tenth parameter that may be measured is respiratory rate. An eleventh

parameter that may be measured expired end-tidal carbon dioxide, such as by routine capnography. A twelfth parameter that may be measured is blood pressure by non-invasive sphygmomanometry. A thirteenth parameter that may be measured is pulse rate or heart rate by manual palpation, electrocardiography ("ECG") or pulse oximetry. A Modified Specific Drug Effect Questionnaire ("MSDEQ") may also be employed as described in '494.

ARCI, POMS and VAS correlate with "liking" of the pharmaceutical preparation administration and may be used to estimate euphoric effects. Pupillary response is associated with mu opoiod activity and pupillary miosis correlates with opioid agonist activity and pupillary dilatation correlates with opioid withdrawal or possibly inverse agonist effects. There are EEG correlates for euphoria (*e.g.*, increased alpha activity as described by Lukas, *et al.* - "EEG alpha activity increases during transient episodes of ethanol-induced euphoria" in *Pharmacology, Biochemistry and Behavior, Vol. 25, No. 4, pp. 889-95, Oct. 1986*, and by Lukas, *et al.*- "Electroencephalographic correlates of marihuana-induced euphoria" in *Drug and Alcohol Dependence, Vol. 37, No. 2, pp. 131-40, Feb. 1995*) and pain (see Chang, *et al.*, "Differential cerebral responses to aversive auditory arousal versus muscle pain: specific EEG patterns are associated with human pain processing" in *Experimental Brain Research, Vol. 147, No. 3, pp. 387-93, Dec. 2002*, and Chang, *et al.*, "Psychophysical and EEG responses to repeated experimental muscle pain in humans: pain activity encodes EEG activity" in *Brain Research Bulletin, Vol. 59, No. 6, pp. 533-43, Feb. 2003*). There is an inverse relationship between respiratory rate and mu opioid agonist activity. There is a proportional or direct relationship between end-tidal carbon dioxide amount and opioid agonist activity. Opioid agonist analgesics tend to decrease resting heart rate and blood pressure, while opioid

withdrawal (as associated with inverse opioid agonist activity in opioid dependent individuals) tends to increase resting heart rate and blood pressure.

The 14 pharmaceutical aliquot preparations containing 6-beta-naltrexol are made up as follows:

Lorcet 10/650 tablets (*Forest Laboratories, Inc., St. Louis, MO*), each containing 10 mg hydrocodone bitartrate and 650 mg acetaminophen, used. Tablets are easily cut in half with the razor blade of a commercially available "pill splitter." 15 tablets are ground up into a powder by mortar and pestal. To it is added 6-beta-naltrexol powder in a pre-measured amount, obtained from Mallinckrodt Chemical of St. Louis, Missouri. To make a 15 mg hydrocodone bitartrate/975 mg acetaminophen/0.5 mg 6-beta-naltrexol preparation, 5 mg of the 6-beta-naltrexol powder is mixed thoroughly with the powder from 10 Lorcet 10/650 tablets. The 5 mg is measured by an A&D brand GX-200 top loading balance (purchased from Spectrum Chemical & Laboratory Products, Gardena, California, catalog number 440-68329). After thorough mixing, the mixed powder from ten Lorcet 10/650 tablets and 5 mg 6-beta-naltrexol powder is measured on the GX-200 balance. One tenth of the measured powder is separated and put into a gelatin-based enterally dissolvable capsule of appropriate size (as can be purchased from a variety of pharmacy compounding supply companies in the United States). To form the other preparations, one simply doubles the amount of 6-beta-naltrexol in each subsequent aliquot until a preparation containing 15 mg hydrocodone bitartrate/975 mg acetaminophen/16 mg 6-beta-naltrexol is arrive at. Ideally, one would add an amount of inert ingredient as needed such that all the capsules have approximately equal mass as measured on the balance, though there is less of a need for this if the experimental protocol calls for placing each capsule in the mouth of the human subject by the experimenter

so as negate the likelihood that human participant will realize any appreciable difference in weight of the capsules, which they will be administered in set time intervals, *e.g.*, every three to six hours or so, or having a time interval approximately equal to the serum half-life of the shortest acting active drug component of the combination pharmaceutical composition.

The subjects given no 6-beta-naltrexol may simply be administered one and one half tablets of Lorcet 10/650 ground by motor and pestal into a powder and placed into a gelatin capsule.

These methods of compounding are "best" only in terms of simplicity for the sake of explanation, are not meant to be interpreted as a best mode of manufacture. Superior methods of manufacture, in light of the present invention, would become apparent to one so skilled in the art of pharmaceutical manufacture.

By collecting and analyzing data in the usual fashion for the above-referenced parameters over time, an approximate of the immediate sub-threshold concentration of 6-beta-naltrexone at steady state, $D_{6BN\text{-}hyd}$, will become readily apparent to one skilled in the art.

Example 4:

The invention described above except that instead of including a neutral receptor binding agent the invention includes a relatively low efficacy opioid agonist analgesic or a partial mu-opioid agonist. This partial mu-opioid agonist may be nalbuphine.

Example 5:

The invention described herein where the opioid agonist analgesic providing for effective analgesia is noroxycodone. This is a significant improvement over prior art

technology in that the advantages of noroxycodone as an analgesic over oxycodone as an analgesic have not been appreciated by those skilled in the art of pharmaceutical manufacture or marketing. Analgesic effects due to the parent oxycodone are primarily kappa opioid receptor mediated (see Ross and Smith, "The intrinsic antinociceptive effects of oxycodone appear to be kappa-opioid receptor mediated" in *Pain, Vol. 73, No. 2, pp. 151-7, Nov. 1997*), while the analgesic effects due to noroxycodone are relatively less kappa opioid receptor mediated, even though noroxycodone may have a relatively lower efficacy than its parent compound. Thus, when oxycodone is administered, there undergoes a transformation, not appreciated until the light of the present invention, whereby there is a transition from relatively more kappa dominated opioid effects to relatively less kappa dominated opioid effect, as the metabolite noroxycodone increases its relative concentration to oxycodone. That this was not appreciated by those very practitioners responsible for oxycodone is evidenced by Kaiko, *et al.* in "Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone" (*Clinical Pharmacology and Therapeutics, Vol. 59, No. 1, pp. 52-61, Jan. 1996*) where the authors conclude "these results support oxycodone, and not oxymorphone [another metabolite of oxycodone], as being responsible for pharmacodynamic and analgesic effects." When oxycodone is initially administered to opioid naïve (oxycodone naïve) humans, there is an increased likelihood of dysphoria and/or nausea/vomiting initially. The present author attributes these initial ill effects to the relative domination of kappa effects, which the author has previously described in *U.S. Patents 5,783,583 and 6,103,258*. As time goes by, the patient "gets used to" being administered oxycodone and the dysphoria, nausea and/or vomiting tend to subside. This, the present invention claims, is due to a relative shift away from kappa effects as oxycodone is converted to noroxycodone.

Example 6:

The invention described herein where the relatively low efficacy opioid agonist analgesic or partial mu-opioid agonist or neutral receptor binding agent is "CTAP" (the D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2 cyclic, penicillamine-containing octapeptide described by Abbruscato, *et al.*, "Blood-Brain Barrier Permability and Bioavailability of a Highly Potent and mu-Selective Opioid Receptor Antagonist, CTAP: Comparison with Morphine" in *The Journal of Pharmacology and Experimental Therapeutics, Vol. 280, No. 1, pp. 402-409, 1997*).

Example 7:

The invention described herein where the relatively low efficacy opioid agonist analgesic or partial mu-opioid agonist or neutral receptor binding agent is xorphanol, described by Gharagozlou, *et al (Ibid).*

Example 8:

The invention described herein where the neutral receptor binding agent is any from the group of 6-alpha-naltrexol, 6-beta-naltrexol, 6-beta-naloxol, 6-beta-naltrexamine and CTAP.

Example 9:

A pharmaceutical composition comprising an opioid agonist analgesic, and any from the group of 6-alpha-naltrexol, 6-beta-naltrexol, 6-beta-naloxol, 6-beta-naltrexamine and CTAP, and a suitable pharmaceutical carrier thereof.

Example 10:

The invention described herein where the where the relatively low efficacy opioid agonist analgesic or partial mu-opioid agonist or neutral receptor binding agent is in the form a peptide that is vulnerable to normal digestion, such that when the combination drug product is ingested the low efficacy opioid agonist analgesic or partial mu-opioid agonist or neutral receptor binding agent is rendered relatively ineffective, allowing for a relative greater preponderance of opioid agonist analgesic effect as compared to when combination drug product is administered parenterally (thus bypassing the digestion of the alimentary tract). This allows for an analgesic composition that is rendered less likely to be abused by being administered parenterally when its intended prescribed route of administration is via the alimentary tract.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that obvious modifications can be made herein without departing from the spirit and scope of the invention. Such variations are contemplated to be within the scope of the appended claims.

I claim by letters patent:

1.) A combination pharmaceutical preparation comprising:

an opioid agonist analgesic;

a neutral receptor binding agent;

and, an acceptable pharmaceutical carrier thereof.

2.) A combination pharmaceutical preparation comprising:

an opioid agonist analgesic;

a partial mu-opioid agonist;

and, an acceptable pharmaceutical carrier thereof.

3.) The invention of Claim 1 where the neutral receptor binding agent is any one from the group consisting of 6-alpha-naltrexol, 6-beta-naltrexol, 6-alpha-naloxol, 6-beta-naloxol, 6-beta-naltrexamine and CTAP.

4.) The invention of Claim 2 where said partial mu-opioid agonist is nalbuphine.

5.) An opioid agonist analgesic composition comprising noroxycodone and a suitable pharmacological carrier thereof.

6.) A combination pharmaceutical preparation comprising:

an opioid agonist analgesic;

CTAP;

and, an acceptable pharmaceutical carrier thereof.

7.) A combination pharmaceutical preparation comprising:

an opioid agonist analgesic;

xorphanol;

and, an acceptable pharmaceutical carrier thereof.

8.) The invention of Claim 1 where said opioid agonist analgesic is any one from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone,

noroxycodone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine and tramadol.

9.) The invention of Claim 2 where said opioid agonist analgesic is any one from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, noroxycodone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine and tramadol.

10.) The invention of Claim 3 where said opioid agonist analgesic is any one from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, noroxycodone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine and tramadol.

11.) The invention of Claim 4 where said opioid agonist analgesic is any one from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine,

diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, noroxycodone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine and tramadol.

12.) The invention of Claim 6 where said opioid agonist analgesic is any one from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone,

ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, noroxycodone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine and tramadol.

13.) The invention of Claim 7 where said opioid agonist analgesic is any one from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, noroxycodone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine,

phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine and tramadol.

14.) The invention of Claim 1, where the neutral receptor binding agent is a peptide.

15.) The invention of Claim 2, where the partial mu-opioid agonist is a peptide.