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(54) **DRUG FORMULATIONS HAVING REDUCED ABUSE POTENTIAL**

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CPC ... A61K 9/167; A61K 9/1676; A61K 9/5078; A61K 9/5073; A61K 31/485

See application file for complete search history.

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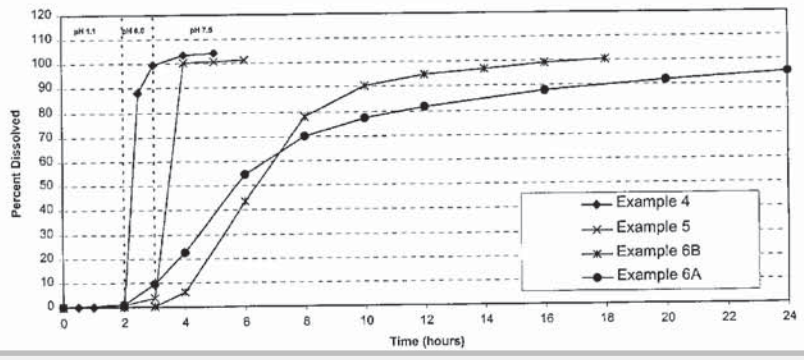
(57) **ABSTRACT**

Drug formulations having reduced abuse potential which contain one or more of (1) a bittering agent, (2) a bright deterrent/indicator dye and (3) fine insoluble particulate matter. The bittering agent and dye are in a form which does not affect proper administration of the drug, but the bittering agent creates a bitter side effect when the dosage form is crushed or chemically extracted and nasally, orally, buccally or sublingually administered and the dye produces a bright color when crushed and contacted. The fine insoluble particulate matter hinders extraction of the drug from the dosage form and, when crushed, can deter intravenous injection because of the presence of the insoluble particles or hinder injection by blocking an intravenous needle. The bright color of the dye, when extracted, also has a psychologically deterrent effect on intravenous abusers.

23 Claims, 1 Drawing Sheet

Mean Dissolution Profiles for Examples 4, 5, and 6



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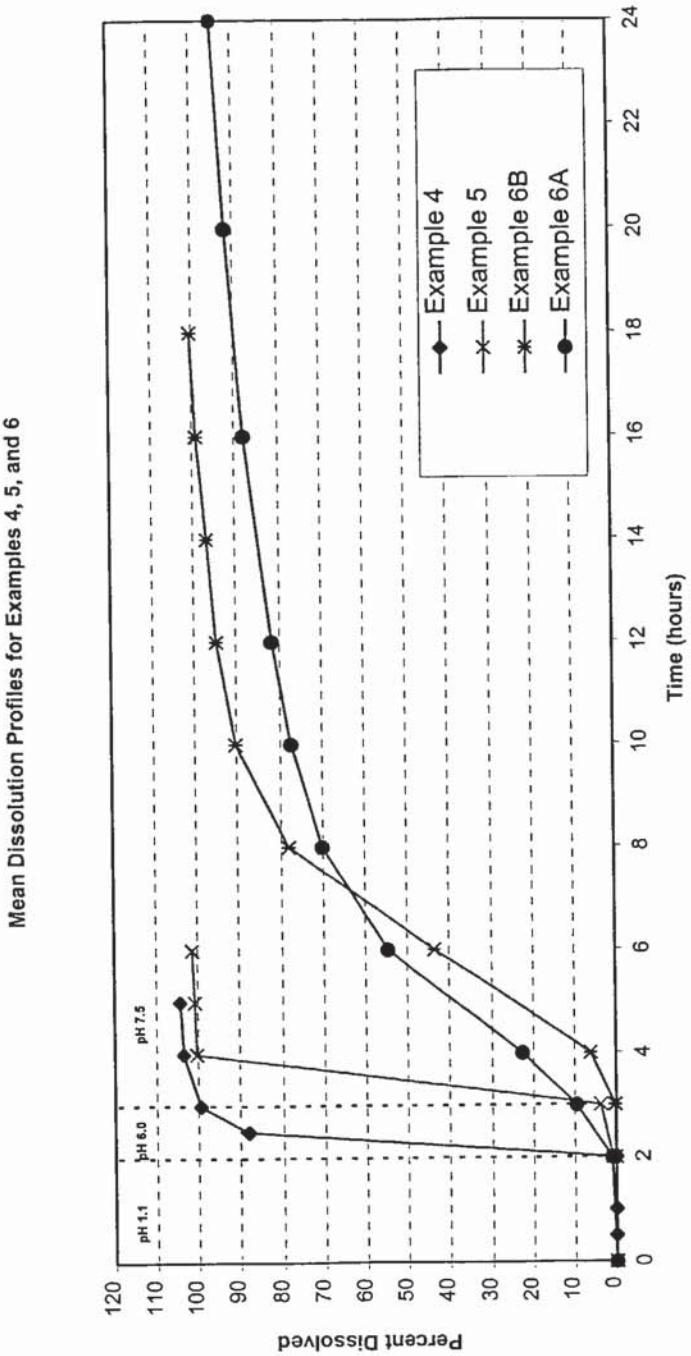

DRUG FORMULATIONS HAVING REDUCED ABUSE POTENTIAL

FIELD OF THE INVENTION

This invention relates to dosage forms of prescription psychoactive drug formulations having a reduced potential for abuse and to methods of reducing the potential for abuse of dosage forms of prescription psychoactive drugs.

BACKGROUND OF THE INVENTION

Prescription psychoactive drugs can help patients manage chronic or severe pain, restore emotional or behavioral balance, control sleep disorders, or fight obesity. When such prescription medications are abused, however, the consequences, including addiction, can be dangerous, even deadly. The risks associated with abuse of three classes of commonly abused prescription drugs, i.e., opioids; central nervous system (CNS) depressants, including sedatives and tranquilizers; and stimulants, are well documented.

Opioids include morphine, codeine, and related drugs such as oxycodone (Percodan and OxyContin), hydrocodone (Vicodin), and meperidine (Demerol) and are commonly prescribed to relieve pain. Taken as prescribed, opioids can be used to manage pain effectively without unwanted side effects. Chronic use of opioids can result in tolerance, which means that users must take higher doses to achieve the same effects. Long-term use also can lead to physical dependence and addiction. Withdrawal can occur when an individual discontinues use of the drugs. Withdrawal symptoms can include restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose humps, and involuntary leg movements. Individuals who are addicted to opioids are more likely to overdose on the drugs, which could be fatal.

Among the most commonly prescribed CNS depressants are barbiturates, such as mephobarbital (Mebaral) and pentobarbital sodium (Nembutal), which are prescribed to treat anxiety, tension, and sleep disorders; and benzodiazepines, such as diazepam (Valium) and alprazolam (Xanax), which typically are prescribed to treat anxiety, acute stress reactions, and panic attacks. Other benzodiazepines, such as triazolam (Halcion) and estazolam (ProSom), are prescribed for short-term treatment of sleep disorders. Although the various classes of CNS depressants work differently, they all produce a beneficial drowsy or calming effect in individuals suffering from sleep disorders or anxiety. However, if one uses these drugs over a long period of time, the body will develop tolerance, and larger doses will be needed to achieve the initial effects. In addition, continued use can lead to physical dependence and, when use is reduced or stopped, withdrawal. Both barbiturates and benzodiazepines have the potential for abuse and should be used only as prescribed. As with opioids, an overdose of these drugs can be fatal.

Stimulants increase heart rate, blood pressure and metabolism, provide feelings of exhilaration and energy, and increase mental alertness. Stimulants such as methylphenidate (Ritalin) and dextroamphetamine (Adderall and Dexedrine) are prescribed for the treatment of narcolepsy, attention-deficit/hyperactivity disorder, and depression that has not responded to other treatments. They also may be used for short-term treatment of obesity. Individuals may become addicted to the sense of well-being and enhanced energy that stimulants can generate. Taking high doses of stimulants

hostility or paranoia. Additionally, taking high doses of stimulants may result in dangerously high body temperatures and an irregular heartbeat.

Abuse potential of these three classes of drugs is of major concern. This is specially true for opioids and stimulants and hence they are classified by the Drug Enforcement Agency (DEA) as Schedule II drugs (substances that have a high potential for abuse with severe liability to cause psychic or physical dependence, but have some approved medical use).

Various dosage forms of psychoactive drugs for medical use are available or possible. These include capsules, tablets, transdermal patches and liquid suspensions. For example, methylphenidate (Ritalin) is available in oral, tablet and extended-release tablet dosage forms. Dextroamphetamine (Adderall) is available in immediate-release tablet and extended-release capsule dosage forms. Methylphenidate, amphetamine, fentanyl, 3-methyl fentanyl, morphine, etorphine, etc. can be incorporated into transdermal patches. A fentanyl patch (Duragesic) is already in the marketplace and a methylphenidate patch (Methypatch) is under FDA review. Liquid suspensions of drugs in immediate release and sustained release forms are also possible. A sustained release system can be formulated by using drug ion-exchange complex particles with a further coating of ethyl cellulose. The ion-exchange technology makes reliable liquid controlled-release possible for many ionic drugs, which include amphetamine, methylphenidate, hydrocodone, codeine, morphine, and the like.

These various dosage forms provide valuable medical benefits when properly taken or administered, but also have a high potential for abuse. For example, sustained release dosage forms are abused by crushing or chewing and then swallowing or snorting or by mixing or dissolving in water or the like and then injecting. Transdermal patches can be chewed to provide a quick onset via buccal, sublingual, or oral absorption of the controlled substances. In addition, a significant drug residue after normal administration of the patches is quite common. Such residue can be extracted and concentrated for abuse. Liquid suspensions can be similarly concentrated and abused.

It view of these problems, new and improved dosage forms of psychoactive drugs having decreased abuse potential are desired. Several approaches to reducing the abuse potential of dosage forms of drugs can be found in U.S. patents. These include, for example, the incorporation of an opioid antagonist into a dosage form (U.S. Pat. Nos. 4,401,672, 4,457,933, 5,162,341, 5,236,714, 6,277,384 and 6,228,863), the use of cytochrome P450 2D6 enzyme inhibitor (U.S. Pat. No. 6,124,282), and the incorporation of a water soluble/gelable material into a dosage form (U.S. Pat. No. 4,070,494). However, these approaches still are far from ideal in terms of the effectiveness of deterring someone from abusing the medication by snorting or improper oral administration.

OBJECT OF THE INVENTION

It is an object of the present invention to reduce the potential for abuse of dosage forms of psychoactive drugs and other drugs of abuse and to provide dosage forms of psychoactive drugs having a reduced potential for abuse. More particularly, it is an object of the present invention to provide oral dosage forms of opioids, CNS depressants and stimulants that have increased effectiveness in deterring abuse by snorting/inject

SUMMARY OF THE INVENTION

According to the present invention dosage forms of psychoactive drugs, which have reduced abuse potential are provided by adding one or more of the following to the dosage forms:

(1) a bittering agent in a form which does not create a bitter taste when a dosage form of the drug is properly administered, but which creates a bitter side effect when the dosage form is crushed or chemically extracted for nasal (snorting), oral, buccal or sublingual administration;

(2) a bright deterrent/indicator dye in a form which does not create color when a dosage form of the drug is properly administered, but which colors or stains the nose, mouth or hands when the dosage form is crushed or chemically extracted; and

(3) fine insoluble particulate matter which does not adversely affect the human body when a dosage form of the drug is properly administered, but which hinders extraction of the drug from the dosage form and can deter intravenous injection because of the presence of the insoluble particles or hinder injection by blocking the intravenous needle.

BRIEF DESCRIPTION OF THE DRAWING

The drawing is a graph showing the mean dissolution profiles of the drug formulations prepared in Examples 4, 5 and 6.

DETAILED EXPLANATION OF THE INVENTION

The psychoactive drug (i.e., a drug that affects the central nervous system) of the dosage form of the present invention is not particularly limited insofar as the drug is approved for medical use in dosage form and has a potential for abuse. The drug includes opioids, central nerve system (CNS) depressants and stimulants such as, for example, drugs sold commercially under the trademarks Adderall XR, Matadate CD, Kadian, Oramorph SR, MS Contin, Oxycontin and the like.

The bittering agent and/or indicator dye to be incorporated into the dosage forms of the present invention is used in a form which does not exhibit its deterrent effect when a dosage form of the drug is properly administered, but exhibits a deterrent effect when the dosage form is chewed, crushed or chemically extracted for nasal (snorting), oral, buccal or sublingual administration. The bittering agent and/or indicator dye can be incorporated into granules, beads, or mini-tablets which can be subsequently coated with a suitable barrier coating to prevent against leakage of the bittering agent and indicator dye and to minimize or prevent absorption of the bittering agent and indicator dye under normal dosage administration conditions. These granules/beads/mini-tablets can be encapsulated or compressed with the drug of interest or can be used as coating substrates for drug layering and further enteric/sustained-release coatings.

The sizes of the granules, beads and mini-tablets is not limited as long as the granules can be incorporated into the dosage forms of the invention. Typically, the granules and beads have a size of 50 μm to 4000 μm. The mini-tablets have a size which is typically significantly smaller than common tablets (<9/32 inch diameter). When granules, beads or mini-tablets containing a bittering agent and/or a dye indicator and not containing a drug are encapsulated with granules, beads of the same size to make it difficult for the respective beads to be distinguished and separated.

Alternatively, the bittering agent and/or indicator dye can be incorporated directly into a drug formulation and the resultant formulation incorporated into granules, beads, or mini-tablets. Subsequently, a barrier coating is applied to ensure against leakage of the bittering agent and indicator dye under normal dosage administration conditions. The resultant coated granules, beads or mini-tablets of the drug formulation are thereafter encapsulated or compressed into tablets.

When used in a transdermal patch formulation, the bittering agent and/or indicator dye can be used in the form of the above-described granules, beads, or mini-tablets coated with a suitable barrier coating. The bittering agent can also be added directly to the transdermal drug formulation.

The bittering agent useful in the present invention includes any pharmaceutically acceptable bitter substance that creates a bitter taste or side effect when administered nasally (snorted), orally, bucally or sublingually. Such agents include, but are not limited to, sucrose octaacetate, denatonium saccharide, denatonium benzoate, caffeine, quinine (or a quinine salt such as quinine sulfate), bitter orange peel oil, and other botanical extract ingredients, such as pepper extract (Cubeb), capsicum, and the like. The preferred bittering agents are sucrose octaacetate, denatonium saccharide and denatonium benzoate because they are inexpensive, show an unusually pronounced bitter tasting effect at low concentrations and are essentially non-toxic in the low concentrations used in the drug formulations of the invention.

Sucrose octaacetate is a USP/NF material and is an intensely bitter compound and has been used in the industry as a bittering agent or a denaturant for alcohol. Denatonium benzoate is the chemical name for Bitrex, an exceptionally bitter substance, which has been added to appropriate home care products. Denatonium saccharide is reportedly four times more bitter than denatonium benzoate. When a product contains sucrose octaacetate, denatonium benzoate or denatonium saccharide, it has such an intensely nasty taste it is practically impossible for a person to ingest it.

The bittering agent is used in an amount of from 0.01 to 10% by weight and, preferably, 0.1 to 4% by weight and, most preferably, 0.1 to 0.5% by weight based on the weight of a dosage form of the pharmaceutical formulation into which the agent is incorporated.

The indicator dye useful in the invention includes any dye that is pharmaceutically acceptable and that is capable of providing an intense, bright color on the nose, mouth and hands after a pharmaceutical formulation containing the dye is crushed or dissolved. The bright color also can have a psychologically deterrent effect on intravenous abusers. Such dyes include, but are not limited to allura red, amaranth, brilliant blue, canthaxanthin, carmine, carmoisine, carotene, curcumin, erythrosine, green S, indigo carmine, iron oxide black, iron oxide red, iron oxide yellow, patent blue, phloxine O, ponceau 4R, quinoline yellow, riboflavin, sunset yellow, tartrazine, titanium dioxide, vegetable carbon black, and other natural colors such as annatto, beet, black carrot, black currant, caramel, carmine, carmine lake, chlorophyll, cochineal, elderberry, grapeskin/grape juice, malt, paprika, red cabbage, turmeric, and anthocyanins. Riboflavin is a preferred indicator because it can also be used as a tracing agent for easy urine detection of drug abusers.

The amount of the dye indicator used in the dosage form of the pharmaceutical formulation will vary with the particular

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