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(54) **ANALGESIC IMMEDIATE AND CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION**

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(58) **Field of Search** 424/464, 468, 424/490, 422, 423, 436, 449, 451, 457, 458, 483, 473, 455, 489, 472, 465, 484, 485, 486, 487, 488

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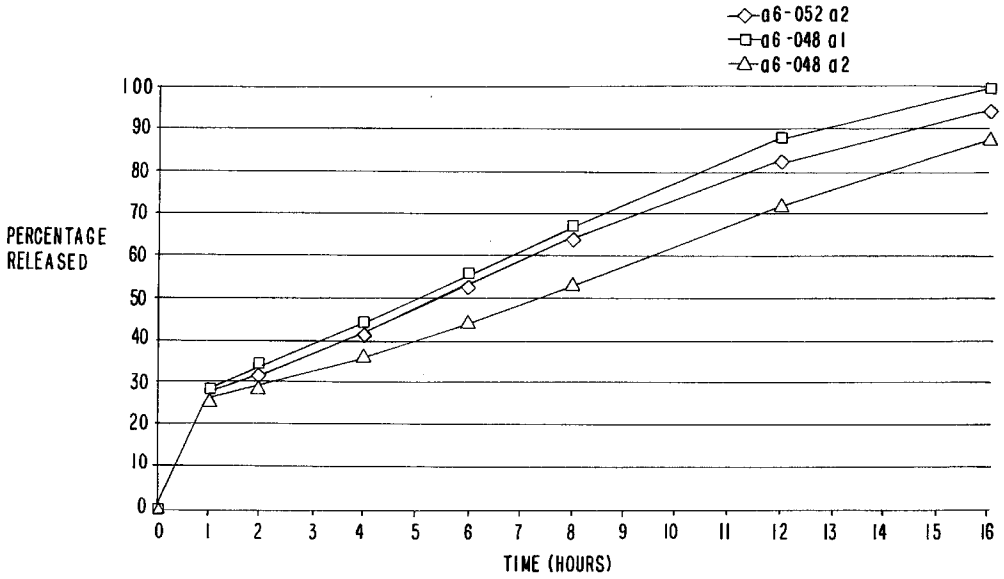
(57) **ABSTRACT**

Disclosed is a method for the therapeutic treatment of pain related to wind up in a human or animal. The method of the invention is practiced by administering to the subject an effective amount of an analgesic pharmaceutical composition which includes a NMDA receptor antagonist in an immediate release form combined with an NMDA receptor antagonist in a sustained release form. The immediate release form and sustained release forn are present in sufficient amounts to diminsh or abolish wind up.

48 Claims, 2 Drawing Sheets



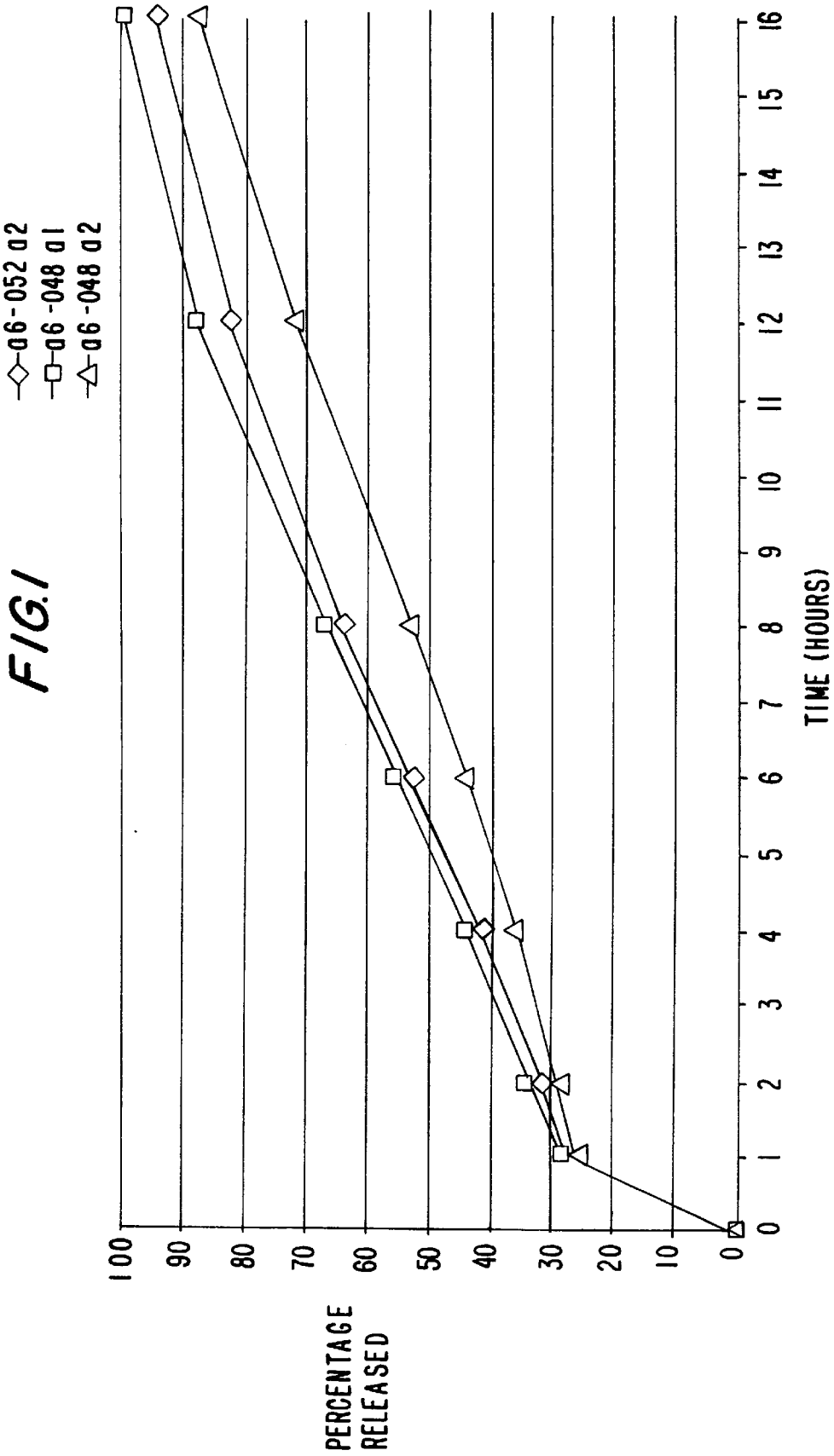


FIG.1

◇ AIM —□—DI3879A2 WATER --●--DI3879A2 pH 1.2 —▲—DI3879A2 pH 6.8

TIME(HR)	AIM	SLOW	FAST	DI3879A2 WATER	DI3879A3 WATER	DI3879A2 pH 1.2	DI3879A2 pH 6.8
0.5	4	0	10	6		0	
2	15	0	29	13		7	6
4	30	15	47	39	14	30	30
6	46	30	65	55	31	50	64
8	60	46	83	82			71
10	78	61	100	83	72	60	80
12	98	80	100	82	75		90
18							100

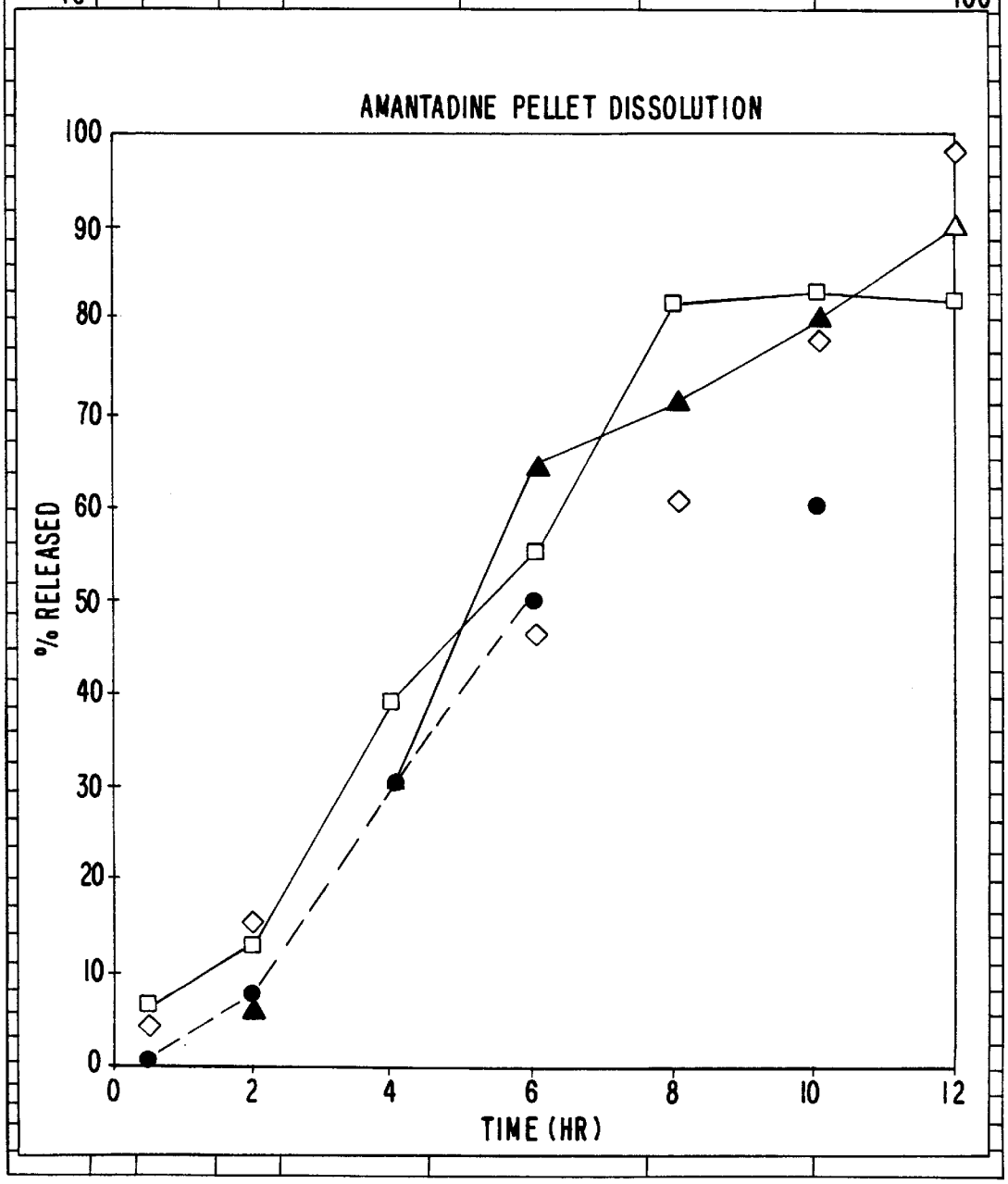


FIG. 2

ANALGESIC IMMEDIATE AND CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION

This application is a continuation of PCT/AU96/00658 filed Oct. 18, 1996.

The present invention relates to pharmaceutical compositions and is particularly concerned with pharmaceutical compositions containing N-methyl-D-aspartate (NMDA) receptor antagonists and their use in the treatment of pain.

BACKGROUND OF THE INVENTION

The amino acid glutamate is an excitatory neurotransmitter that is an agonist at many post-synaptic terminals of the central nervous system. The glutamate receptor complex is termed the NMDA receptor and is a potential target for therapeutic drugs. This receptor incorporates an ion channel complex which is novel because it is gated by both dual ligand binding (glutamate and glycine) and membrane voltage. Because of the novel requirements for activation, it is believed that the NMDA receptor complex plays only a minor role in routine synaptic transmission. However, the receptor complex may be activated following repeated afferent stimuli as occurs during trauma such as surgery. Repeated stimuli cause a temporal summation of C-fibre-mediated responses of dorsal horn nociceptive neurones; this phenomenon, increased output to a constant input, is known as wind-up.

Studies indicate that activation of the NMDA receptor complex in the spinal dorsal horn leads to increased spontaneous neural discharge, expanded receptive fields and exaggerated responses to afferent input. These neural mechanisms may be expressed physically as hyperalgesia (increased pain sensation) and allodynia (pain arising from a stimulus that is not normally painful).

Opioids, through their ability to inhibit release of primary afferent neurotransmitters or to inhibit interneurons early in nociceptive pathways, initially reduce or block C-fibre inputs to the deeper dorsal horn nociceptive neurones. However, as the peripheral stimulation continues, wind-up breaks through the input inhibition and the neurones start to respond. Thus at moderate doses, opioids delay the onset of wind-up without inhibiting the process itself.

By contrast, NMDA receptor antagonists have no effect on the initial inputs to the cells but diminish or abolish wind-up and convert the potentiated response to a normal response.

We have found that a particularly effective composition for the administration of an NMDA receptor antagonist to diminish or abolish wind up is one providing both immediate release of an NMDA receptor antagonist and controlled or sustained release of an NMDA receptor antagonist.

NMDA antagonist receptors have also been indicated to be effective in the treatment of Huntington's disease, amyotrophic lateral sclerosis (ALS), AIDS-related dementia, Alzheimer's disease, schizophrenia, motoneurone diseases and CNS and brain injuries resulting from a number of causes including stroke, trauma and neurosurgery.

THE INVENTION

In accordance with one aspect of the present invention there is provided a pharmaceutical composition for the administration of an NMDA receptor antagonist to a human or animal subject, the composition including an NMDA receptor antagonist in an immediate release form in association with an NMDA receptor antagonist in a controlled release form.

The same NMDA receptor antagonist may be used in both the immediate and controlled release forms or they may be different NMDA receptor antagonists.

The composition of the invention is suitable for the treatment of chronic or acute pain, for example to be administered pre-operatively.

Accordingly, the present invention further provides a method for the therapeutic or prophylactic treatment of pain in a human or animal subject, the method including administering to the subject, a composition in accordance with the present invention. The method of the invention may be used to treat chronic or acute pain.

The composition of the invention may be used in the pre-emptive treatment of pain. The various features of novelty which characterize the invention are pointed out with particularity in the claims next to and form a part of the specification. For a better understanding of the invention, its operative advantages and specific objects obtained by its use, reference should be had to the accompanying drawings and descriptive matter in which there is illustrated and described in the preferred embodiment of the invention.

Preferably the NMDA receptor antagonist may be selected from a morphinan such as dextromethorphan and dextrorphan, ketamine, amantadine, memantine, eliprodil, ifenprodil, dizocilpine, remacemide, iamotrigine, riluzole, aptiganel, phencyclidine, flupirtine, celfotel, felbamate, spermine, spermidine, levemopamil, a pharmaceutically acceptable salt or ester thereof, or a metabolic precursor of any of the foregoing.

The formulation may include sufficient NMDA receptor antagonist to provide from about 1–5000 mg/day, typically 1–1000 mg/day and preferably about 100–800 mg/day of the active ingredient. The composition includes an NMDA receptor antagonist in an immediate release form in association with a NMDA receptor antagonist in a controlled release form. The composition may include an amount of NMDA receptor antagonist in the immediate release form of approximately 5% to 90% of the total NMDA receptor antagonist, preferably 10% to 60%. An immediate release NMDA receptor antagonist content of about 15% to 50% is particularly preferred. The controlled release form of the NMDA receptor antagonist may constitute the remainder of the active ingredients.

The composition of the invention may be in a form suitable for oral or rectal administration or for administration by transdermal, intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular means.

The composition of the invention may or may not be in a single dosage form. Preferably the composition is in a single dose form.

The composition may be formulated as an oral dosage form such as a tablet, capsule, a liquid, powder, granule or suspension, an injectable solution, a suppository, implant or transdermal patch.

Preferably the NMDA receptor antagonist is dextromethorphan (DM) or a pharmaceutically acceptable salt thereof. Preferably the dextromethorphan is in the form of dextromethorphan hydrobromide.

The oral form of the pharmaceutical compositions of the invention may be selected from:

1) liquids, for example, suspensions, reconstitutable powders, elixirs, oils, solutions,or emulsions;
2) confectionery, for example, chewing gums, lozenges or candy bars;
3) powders, for example, drug powder, prilled material, coated actives or granulated materials;
4) capsules, for example, soft gelatin, hard gelatin containing, pellets, powders, tablets, granulates, liquids, or combinations of these; said capsules may or may not be coated;
5) tablets, for example, disintegrating, chewable effervescent, matrix, osmotic pumps, prepared by multi-layering, contain coated powders in tablets, tablets in tablets, pellets in tablets etc, said tablets may or may not be coated.

The oral pharmaceutical composition of the invention may be in the form of a "taste-masked" or "taste-neutral" form.

The method of manufacture, components and quantities of components used, depend on the particular pharmaceutical composition being considered.

A suitable immediate release (IR) form of the NMDA receptor antagonist may simply be particles of the antagonist or particles of the antagonist admixed with soluble components for example, sugars (eg sucrose, lactose, fructose, mannitol etc.), polymers (eg polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, etc), surfactants (sodium lauryl sulphate, chremophor, tweens, spans, pluronics, and the like), insoluble components (microcrystalline cellulose, Ca_3 $(PO_4)_2$, talc, fumed silica, i.e. aerosil® and the like), coating material (examples of suitable coating materials are polyethylene glycol, hydroxypropyl methyl cellulose, wax, fatty acids, etc.), dispersions in suitable material (examples are wax, polymers, pharmaceutically acceptable oils, soluble agents etc) or combinations of the above. These mixtures may be prepared by blending, mixing, dissolution and evaporation, or by using suspensions etc. These mixtures may be deposited on inert cores, wet massed and extruded, granulated, spray dried, etc. These mixtures or processed mixtures may be used in suspensions, filled into capsules, tabletted, filled into sachets, used in confectionery and so on.

The controlled release may be a sustained release or delayed/modified release.

A controlled-release dosage form as defined in US Pharmacopeia XXII includes extended release dosage forms which allow at least a twofold reduction in dosing frequency as compared to the drug presented as a conventional dosage form and delayed release dosage forms which release the drug at a time other than promptly after administration.

A core used herein the description contains the active ingredient and other carriers and excipients, fillers, stablising agents, binders, core seeds or colorants. The active component may be present in amounts of approximately 0.1 to 95% by weight based on the weight of the total core element. Preferably the active components is present in amounts of 10 to 80% by weight based on the weight of the total core element. The core may be 200 to 1700μ in diameter.

A pellet is a coated core, the coating being any suitable coating.

Preferably, the controlled release component is a sustained (or extended) release form.

A suitable sustained release (SR) form of the NMDA receptor antagonist may be a matrix tablet composition. Suitable matrix forming materials are waxes (eg. carnauba, bees wax, paraffin wax, ceresine, shellac wax, fatty acids, fatty alcohols), oils, hardened oils or fats (eg. hardened rapeseed oil, castor oil, beef tallow, palm dil, soya bean oil), polymers (eg. hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, polyethylene glycol) and other excipients known to those familiar with the art. Other suitable matrix tabletting materials are microcrystalline cellulose, powdered cellulose, hydroxypropyl cellulose, ethyl cellulose, with other carriers, fillers, and excipients known to those familiar with the art. SR tablets may contain granulates, coated powders, pellets, or be multi-layered and the finished tablet may be coated or uncoated.

Suitable coating materials to prepare SR products are any pharmaceutically acceptable polymer such as ethyl cellulose, cellulose acetate butyrate, cellulose acetates, polymethacrylates containing quaternary ammonium groups or other pharmaceutically acceptable polymers, polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, and monomeric materials such as sugars including lactose, sucrose, fructose and mannitol, salts including sodium chloride, potassium chloride and derivatives, organic acids including fumaric acid, succinic acid, lactic acid and tartaric acid and mixtures thereof, enteric polymers including hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, shellac, zein, and polymethacrylates containing carboxyl groups. These polymers may be applied as solutions or latexes. Other barriers may be used such as waxes.

The coating composition may or may not be plasticised according to the properties of the coating blend such as the glass transition temperature of the main component or mixture of components or the solvent used for applying the coating compositions. Suitable plasticises can be added from 0 to 50% by weight of the coating composition and at least one may be selected from diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, castor oil and the like.

Cores containing active may be coated directly to produce a SR dose, or tablets or capsules containing active may be coated.

A suitable SR form of NMDA receptor antagonist may be an osmotic pump, or combinations of the above.

These IR or SR forms may be made by prilling, spray drying, pan coating, melt granulation, granulation, wurster coating, tangential coating, top spray, tabletting, extruding, coacervation and the like.

The particle sizes of the IR and SR components in the dosage form depends on the technology used. The particle

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