This invention relates to novel salts of Nefopam, which may be suitable for use in therapy.
NEW SALTS

Field of the Invention

This invention relates to novel salts of a known compound, which may be suitable for use in therapy.

Background of the Invention

Nefopam is a centrally acting non-narcotic analgesic not structurally related to other analgesics. Nefopam has been shown to induce antinociception in animal models of pain and in humans (reviewed in Heel et al., Drugs 19(4): 249-67, 1980). However, nefopam is not active in the mouse tail-flick test, the hot plate test or the Randall-Selitto pressure test in rats (Conway and Mitchell, Arch. Int. Pharmacodyn. Ther. 226(1): 156-71, 1977), suggesting that its analgesic mechanism is not opiate-like or anti-inflammatory in nature. Nefopam's antinociception is not blocked by nalaxone, further suggesting that its analgesic action is not through opiate receptors.

In vitro and in vivo studies with nefopam enantiomers have shown that (+)-nefopam has more potent analgesic and dopamine, norepinephrine and serotonin-uptake inhibitory properties than (-)-nefopam, with the order of potency given as (+)-nefopam > (±)-nefopam > (-)-nefopam (Fasmer et al., J.Pharm. Pharmacol. 42(6): 437-8, 1987; Rosland and Hole, J. Pharm. Pharmacol. 42(6): 437-8, 1990; Mather et al., Chirality 12(3): 153-9, 2000). Mather et al. (2000) conclude that "...there is currently no compelling rationale to justify administering or monitoring individual enantiomers [of nefopam]."

Nefopam has also been shown to be opiate-sparing when given with morphine in trials of patient-controlled analgesia (Mimoz et al., Anaesthesia 56(6): 520-5, 2001).

Conventional release preparations of racemic nefopam hydrochloride have been commercially available for many years, for use in treating moderate to severe pain. However, the short elimination half-life of nefopam (four hours) means that it is difficult to maintain analgesic efficacy over the normal dosing period (three times daily). Dose escalation of nefopam brings about an increase in the frequency of adverse drug reactions associated with the analgesic, and adverse effects on pulse and blood pressure have been observed following parenteral delivery of therapeutic doses of nefopam (Heel et al., 1980). Chronotropic and ionotropic effects on the heart are not present when nefopam is administered orally (Bhatt et al., Br. J. Clin. Pharmacol. 11(2): 209-1 1, 1981).
Nausea and vomiting are side-effects of the use of many drugs, including those administered for the treatment of pain. WO03/105832 discloses the use of (+)-nefopam for the treatment of nausea, dizziness, blurred vision and emesis. WO03/105833 discloses the use of (+)-nefopam in the treatment of pain by intranasal administration.

WO2005/056539 discloses an efficient process for the production of (+)-nefopam, by resolution of a mixture of the enantiomers, using O,O-dibenzoyl-L-tartaric acid as the resolving agent.

It is well known that racemic nefopam hydrochloride preferentially crystallises in the anhydrous form (Glaser et al, J. Pharm. ScL, 1986, 75(8), 772-4; Glaser et al, JCS, Perkin Tans. 2 1989, 113-122 and Hansen et al, Acta Chemica Scand., Ser. B, 1984, 327-9), whilst the single isomers of nefopam hydrochloride preferentially crystallise as a monohydrate. We have found that anhydrous forms of (+)-nefopam hydrochloride readily convert to the monohydrate at moderate humidity, for example 30 - 50% relative humidity. The monohydrate is stable at moderate humidity, for example above about 25% relative humidity. At lower humidity the monohydrate transforms into one of the anhydrous forms. It is also possible to convert the monohydrate into an anhydrous form by thermal means, for example by heating at about 130°C for about 10 minutes. We have found that during the manufacture of (+)-nefopam hydrochloride monohydrate a mixture of the desired form and anhydrous forms may result. This may be due to poor control of the crystallisation process or by inadvertent over drying of the product. A conventional tableting procedure may also cause drying. Either way, an alternative salt form of (+)-nefopam is desirable.

**Summary of the Invention**

The present invention is based on the surprising discovery that salts of (+)-nefopam, and therefore also of (-)-nefopam, can be formed which are not hydrated. More particularly, we have found salts of (+)-nefopam that are not hygroscopic over the range of 20 - 85%, preferably 20-80% relative humidity. In a first embodiment, the present invention provides a salt of (+)-nefopam, having a water uptake of less than 10% at 80% relative humidity. In a second embodiment, the present invention provides a salt of (+)-nefopam, having a water uptake of less than 5% at 85% relative humidity.
In further embodiments, the present invention provides (+)-nefopam as the fumarate salt, (+)-nefopam as the maleate salt, (+)-nefopam as the sulphate salt, (+)-nefopam as the phosphate salt, (+)-nefopam as the glutamate salt and (+)-nefopam as the besylate salt.

The present invention further provides pharmaceutical compositions comprising a compound as herein described, and a pharmaceutically acceptable excipient, diluent or carrier.

The present invention further provides the salts and pharmaceutical compositions described herein for use in prophylaxis or therapy.

The salts of the present invention may be used to treat the following conditions: depression and depressive disorders, post-traumatic stress disorders, attention-deficit disorders, obsessive compulsive disorders, anxiety disorders, eating disorders, pre-menstrual syndrome, substance abuse, micturition disorders, IBS, fibromyalgia, sexual dysfunction, acute, chronic or neuropathic pain (including, but not limited to, pain associated with cancer, surgery, arthritis, dental surgery, painful neuropathies, trauma, musculoskeletal injury or disease, visceral diseases), dysmenorrhoea, migraine headache and emesis, including acute, delayed, post-operative, last-phase and anticipatory emesis.

The salts of the present invention may be co-administered (simultaneously, sequentially or separately) with an opiate or an analgesia inducer selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug, a narcotic analgesic, a local anesthetic, an NMDA antagonist, a neuroleptic agent, an anti-convulsant, an anti-spasmodic, an anti-depressant, a muscle relaxant and mixtures thereof.

When the condition treated is emesis, it may have been induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorder, motion, post-operative sickness, surgery, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, migraine, opioid analgesics, or mixtures thereof.

Controlled or delayed release formulations comprising the nefopam salts of the present invention are also contemplated.

Description of Preferred Embodiments

As used herein, "nefopam" refers to a compound of formula I.
as well as the (+) and (-) enantiomers which are as far as possible optically pure. (+)-Nefopam may be preferred, for reduced side-effects when used in therapy (and which may be caused by drug-drug interaction).

Preferred salts according to the present invention are the fumarate, maleate, succinate, sulphate, phosphate, toluenesulphonate, benzene sulphonate and methane sulphonate. Other salts which meet the water uptake criterion can readily be prepared, e.g. on the basis of the protocols described herein, and tested by standard procedures.

A salt according to the invention may be used in therapy, e.g. as described in WO03/105832 and WO03/105833, as well as in therapies described in new British Patent Applications filed in the name of Sosei R&D Ltd.; the contents of these documents are incorporated herein by reference.

The compounds of formula (1) can be used among other things in the treatment of pain (acute, chronic or neuropathic pain including, but not limited to, pain associated with cancer, surgery, arthritis, dental surgery, painful neuropathies, trauma, musculoskeletal injury or disease, visceral diseases, IBS, dysmenorrhoea or migraine headache), emesis, depression, post-traumatic stress disorders, attention-deficit disorders, obsessive compulsive disorders, eating disorders, anxiety disorders, pre-menstrual syndrome, substance abuse, micturition disorders, IBS, fibromyalgia and sexual dysfunction.

When used in therapy, a salt according to the invention may be given by any suitable route of administration in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. For example, any of oral, topical, buccal, sublingual, ocular, rectal, parenteral, vaginal, inhalation and intranasal delivery routes may be suitable. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrastemal injection or infusion techniques. The dose of the active agent will depend on the nature and degree of the condition, the age and
condition of the patient, and other factors known to those skilled in the art. A typical dosage is 1-200 mg given one to three times per day.

We have found that compounds of formula (1) have a fast onset of action and are therefore desirable for the treatment of conditions in which standard treatments are associated with long onset of therapeutic effect.

Controlled release may extend the therapeutic effect and reduce the occurrence of side-effects associated with plasma peak concentrations of an immediate release product. If controlled release of the active agent is required, a suitable formulation of any type known to those skilled in the art may be used. Modified release can be afforded by either dissolution or diffusion controlled monolithic devices, beaded encapsulated systems, osmotically controlled systems, and modified film coating systems incorporating suitable polymeric and non-polymeric hydrophilic and hydrophobic materials. Suitable controlled-release formulations include hydrophilic materials comprising, but not limited to, acrylic or methacrylic polymers or copolymers, alkylviny polymers, celluloses, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, alginates, pectins, starches and derivatives, natural and synthetic gums, polycarbophil and chitosans. Suitable hydrophobic materials comprise, but are not limited to, the group consisting of hydrophobic polymers, waxes, fats, long-chained fatty acids, their corresponding esters, their corresponding ethers, and their mixtures.

The following examples substantiate the invention

Experimental

(+) Nefopam may be obtained in a number of ways that have previously been disclosed. For example, Isaksson et al (J. Pharm. Pharmacol., 1998, 40, 48-50) have disclosed the preparation of (+)-nefopam by chiral liquid chromatography. WO2005/056539 discloses an efficient process for the production of (+)-nefopam, by resolution of a mixture of the enantiomers, using O,O-dibenzoyl-L-tartaric acid as the resolving agent. Either process or other processes obvious to one skilled in the art are suitable for the preparation of (+)-nefopam (or (-)-nefopam) for the preparation of the disclosed salts.

(+) Nefopam fumarate

The following procedure describes the conversion of (+)-nefopam hydrochloride to (+)-nefopam monofumarate. It will be clear to one skilled in the
that the prior formation of the hydrochloride salt is not a necessary step in the preparation of (+)-nefopam fumarate.

Potassium carbonate (433 g, 1.6 eq) is added to a suspension of AD 337 hydrochloride monohydrate (97% e.e.; 613.6 g, 2 mol) in toluene (1800 ml) and water (600 ml). The mixture is stirred at 50 - 55°C for one hour. The organic layer is separated, washed with water (1000 ml) and concentrated under vacuum. The product is taken up in ethanol (600 ml) and concentrated under vacuum to give clear oil.

The oil from above is taken up in ethanol (5000 ml) and water (44 ml). After addition of fumaric acid (231.5 g, 2 mol, 1 eq) the mixture is heated at 70°C to ensure dissolution. The mixture is filtered at this temperature to remove any insoluble impurities and cooled to 0°C. The product is filtered, washed with ethanol (700 ml) at 0°C and dried under vacuum for 6 -8 hours to furnish (+)-nefopam monofumarate 635 g, 84%.

The ¹H NMR spectrum and elemental analysis were in agreement with the assigned structure. The fumarate salt showed less than 0.1% mass change up to 85% relative humidity.

(+)-nefopam maleate

(+)-Nefopam (500 mg) and maleic acid (229 mg) were dissolved in ethyl acetate (94 ml) and treated with ultrasound. The salt precipitated as a white solid.

The ¹H NMR spectrum and elemental analysis were in agreement with the assigned structure. The maleate salt showed less than 1% mass change up to 85% relative humidity.

(+)-nefopam sulphate

(+)-Nefopam (500 mg) and sulphuric acid (3.95 ml) were mixed and the solution evaporated with ultrasonic treatment. The resultant oil was dissolved in THF (100 µl) and evaporated with ultrasonic treatment a second time and kept under vacuum overnight. 2-Propanol (400 µl) was added to the amorphous solid and the mixture stirred with temperature cycling. The hot mixture (50°C) was filtered and washed with toluene to afford (+)-nefopam sulphate.

(+)-nefopam phosphate

(+)-Nefopam (500 mg) and 0.5 M phosphoric acid (3.95 ml) were mixed and the solution evaporated with ultrasonic treatment and kept under vacuum
overnight. 2-Propanol (2 ml) was added to the amorphous film and the mixture stirred with temperature cycling. The solid was filtered and washed with toluene.

The $^1$H NMR spectrum and elemental analysis were in agreement with the assigned structure. The phosphate salt showed less than 3% mass change up to 80% relative humidity.

The $^1$H NMR spectrum and elemental analysis were in agreement with the assigned structure. The sulphate salt showed less than 10% mass change up to 80% relative humidity.
CLAIMS
1. A salt of (+)-nefopam, having a water uptake of less than 10% at 80% relative humidity.
2. A salt according to claim 1, having a water uptake of less than 5% at 80% relative humidity.
3. A salt according to claim 1, having a water uptake of less than 2% at 80% relative humidity.
4. A salt according to claim 1, having a water uptake of less than 1% at 80% relative humidity.
5. A salt of (+)-nefopam, having a water uptake of less than 10% at 85% relative humidity.
6. A salt according to claim 5, having a water uptake of less than 5% at 85% relative humidity.
7. A salt according to claim 5, having a water uptake of less than 2% at 85% relative humidity.
8. A salt according to claim 5, having a water uptake of less than 1% at 85% relative humidity.
9. A salt of (+)-nefopam, having a water uptake of less than 10% at 95% relative humidity.
10. A salt according to claim 9, having a water uptake of less than 5% at 95% relative humidity.
11. A salt according to claim 9, having a water uptake of less than 2% at 95% relative humidity.
12. A salt according to claim 9, having a water uptake of less than 1% at 95% relative humidity.
13. A salt according to claim 9, having a water uptake of less than 0.5% at 95% relative humidity.
14. (+)-nefopam as the fumarate salt.
15. (+)-nefopam as the maleate salt.
16. (+)-nefopam as the sulphate salt.
17. (+)-nefopam as the phosphate salt.
18. A pharmaceutical composition comprising a compound according to any of claims 1 to 17 and a pharmaceutically acceptable excipient, diluent or carrier.
19. A compound according to any of claims 1 to 17, or a composition according to claim 18, for use in prophylaxis or therapy.
20. Use of a compound according to any of claims 1 to 17 for use in the manufacture of a medicament for use in prophylaxis or therapy, wherein the compound is optionally combined with a pharmaceutically acceptable excipient, diluent or carrier.

21. A compound according to claim 19 or the use according to claim 20, wherein the condition is selected from the group consisting of depression and depressive disorders, post-traumatic stress disorders, attention-deficit disorders, obsessive compulsive disorders, anxiety disorders, eating disorders, pre-menstrual syndrome, substance abuse, micturition disorders, IBS, fibromyalgia, sexual dysfunction, and mixtures thereof.

22. A compound according to claim 19 or the use according to claim 20, wherein the condition is selected from the group consisting of acute, chronic or neuropathic pain (including, but not limited to, pain associated with cancer, surgery, arthritis, dental surgery, painful neuropathies, trauma, musculo-skeletal injury or disease, visceral diseases), dysmenorrhea, migraine headache and mixtures thereof.

23. Use according to any of claims 20 to 22, wherein the subject is also treated with an opiate.

24. Use according to any of claims 20 to 23, wherein the subject is also treated with an analgesia inducer selected from the group consisting of acetaminophen, a non-steroidal anti-inflammatory drug, a narcotic analgesic, a local anesthetic, an NMDA antagonist, a neuroleptic agent, an anti-convulsant, an anti-spasmodic, an anti-depressant, a muscle relaxant and mixtures thereof.

25. Use according to any of claims 20, 23 or 24, wherein the condition is emesis.

26. Use according to claim 25, wherein the emesis is selected from acute, delayed, post-operative, last-phase and anticipatory emesis.

27. Use according to claim 25, wherein the emesis is induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorder, motion, post-operative sickness, surgery, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, migraine, opioid analgesics, or mixtures thereof.

28. Use according to any of claims 20 to 27, wherein the medicament provides controlled or delayed release of the nefopam salt.
29. A controlled or delayed release dosage form comprising a nefopam salt according to any of claims 1 to 17 or a composition according to claim 18.