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(54) **FORMULATION**

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(57) **ABSTRACT**

Aqueous formulations suitable for intranasal administration comprise buprenorphine or a physiologically acceptable salt or ester thereof and (a) a pectin having a degree of esterification of less than 50%, (b) chitosan and a polyoxyethylene-polyoxypropylene copolymer (poloxamer) or (c) chitosan and hydroxypropylmethylcellulose. Such formulations can induce rapid and prolonged analgesia when delivered intranasally to a patient. The buprenorphine or buprenorphine salt or ester may be delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration of buprenorphine, C_{ther} , of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours.

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FIGURE 1

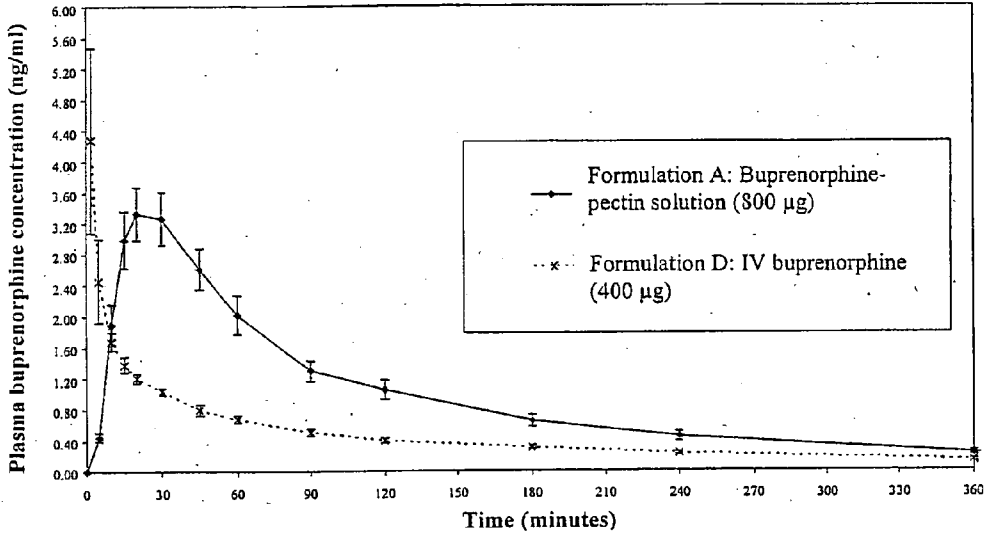


FIGURE 2

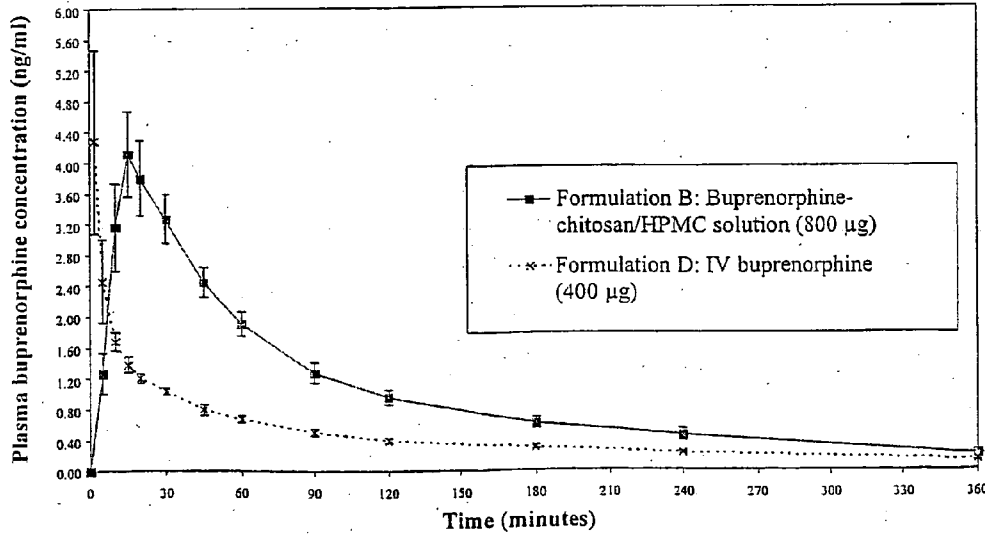


FIGURE 3

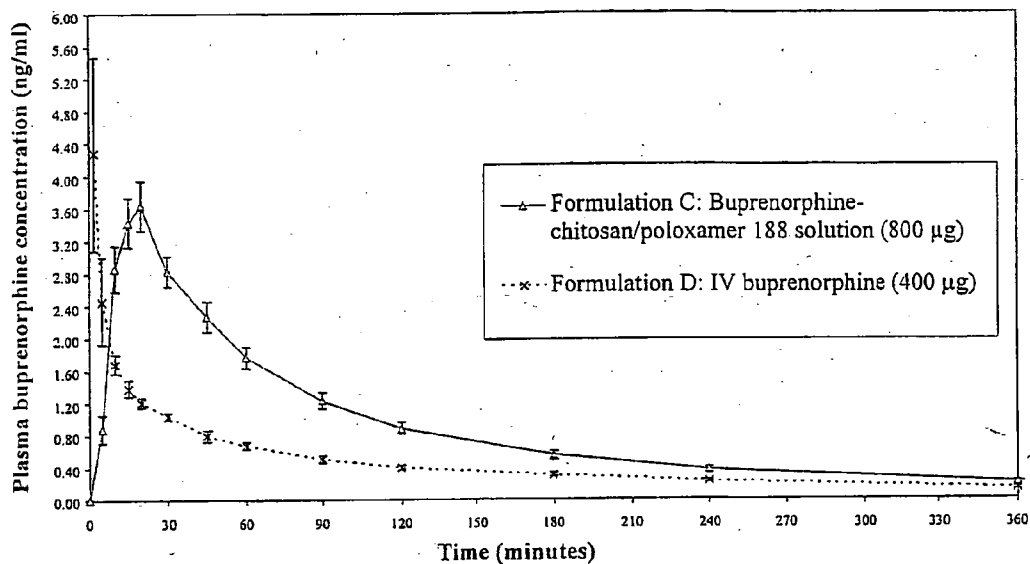
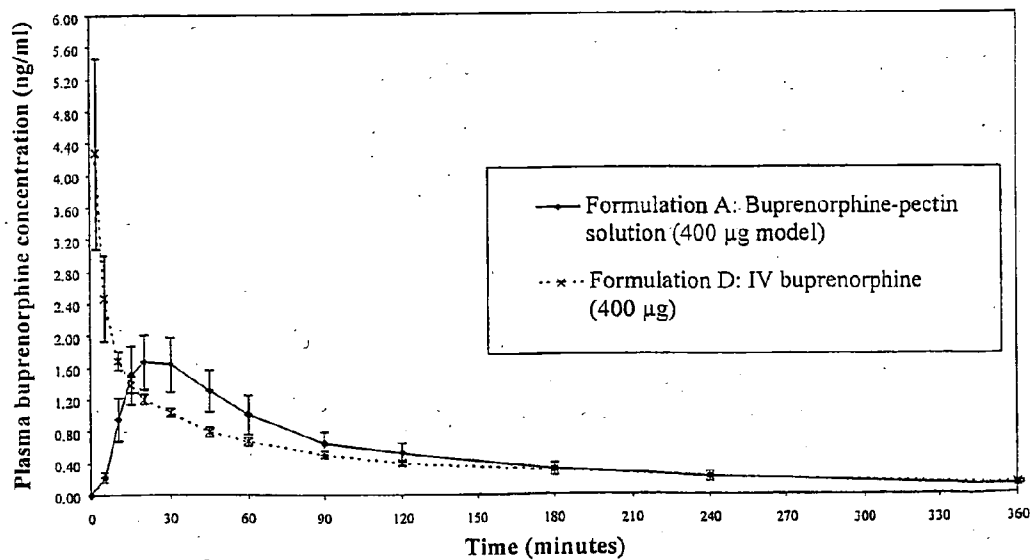


FIGURE 4



FORMULATION

FIELD OF THE INVENTION

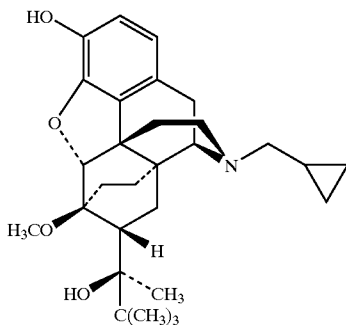
[0001] The invention relates to pharmaceutical formulations of buprenorphine and physiologically acceptable salts and esters thereof.

BACKGROUND OF THE INVENTION

[0002] The term opioid (or opiate) defines drugs with morphine-like properties. Opioids can be sub-classified on the basis of their receptor specificity. Mu-agonist opioids provide intense analgesia. These opioids can be long-acting (e.g. methadone) or short-acting (e.g. remifentanyl).

[0003] Mixed agonist/antagonist opioids (e.g. butorphanol and buprenorphine) are partial agonists (the former at mu and kappa receptors and the latter at the mu receptor) and can produce good quality analgesia. They produce less respiratory depression and constipation than high efficacy mu agonists.

[0004] Buprenorphine (CAS RN 52485-79-7; [5 α ,7 α (S)-17-(Cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-6,14-ethenomorphinan-7-methanol) has the formula:



[0005] The hydrochloride is also active (CAS RN 53152-21-9).

[0006] Buprenorphine is a highly lipophilic derivative of thebaine. It is a partial mu agonist and mediates analgesia at the mu opioid receptor. Buprenorphine produces a similar maximum analgesic effect to full mu agonists such as morphine in animal models of pain and, although it may have a ceiling effect in certain pain types in man, it has been shown to produce good quality analgesia of similar efficacy to morphine in most clinical situations including severe pain. An unusual property of buprenorphine observed in in vitro studies is its very slow rate of dissociation from its receptor.

[0007] As a class, opioids are associated with a number of undesirable side-effects, including respiratory depression, nausea, vomiting, dizziness, mental clouding, dysphoria, pruritus, constipation, increased biliary tract pressure, urinary retention and hypotension. The development of tolerance and the risk of chemical dependence and abuse are further problems. Buprenorphine, however, is unusual in

first increases with larger doses, reaches a ceiling and then diminishes as the dosage is further increased, which makes it a safer drug than morphine, where respiratory depression will ultimately lead to death. Buprenorphine has also been shown to have a lower incidence of other side-effects like constipation in man, and it has a lower abuse potential than full mu agonists.

[0008] Buprenorphine has previously been administered via the intravenous, intramuscular and sublingual routes to human subjects. There are limited reports of nasal administration. Eriksen et al, J. Pharm. Pharmacol. 41, 803-805, 1989 report administration to human volunteers of a nasal spray. The spray consisted of 2 mg/ml of buprenorphine hydrochloride dissolved in 5% dextrose and the pH of the solution was adjusted to pH 5.

[0009] WO 90/09870 describes a composition for administration to mucosa comprising a pharmacologically active compound and a polycationic substance such as DEAE-dextran or chitosan. WO 98/47535 discloses a single component liquid pharmaceutical composition for administration to a mucosal surface. The composition comprises a therapeutic agent, a pectin with a low degree of esterification and an aqueous carrier that gels or can be adapted to gel at the site of application. Neither WO 90/09780 nor WO 98/47535 mentions buprenorphine.

SUMMARY OF THE INVENTION

[0010] Improved buprenorphine formulations for nasal administration have now been devised. Rapid uptake of the buprenorphine across the nasal mucosa into the plasma can be achieved, which results in fast onset of analgesia. Further, the residence time of the buprenorphine in the nasal cavity can be increased, which results in prolonged analgesia. An improved profile of absorption of buprenorphine into the systemic circulation can thus be achieved by use of the formulation. Accordingly, the present invention provides:

[0011] (1) an aqueous solution suitable for intranasal administration, which comprises from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof and from 5 to 40 mg/ml of a pectin having a degree of esterification of less than 50%; which solution has a pH of from 3 to 4.2, is substantially free from divalent metal ions and gels on the nasal mucosa;

[0012] (2) an aqueous solution suitable for intranasal administration, which comprises:

[0013] (a) from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof,

[0014] (b) from 0.1 to 20 mg/ml of a chitosan, and

[0015] (c) from 0.1 to 15 mg/ml of hydroxypropylmethylcellulose (HPMC);

[0016] which solution has a pH of from 3 to 4.8; and

[0017] (3) an aqueous solution suitable for intranasal administration, which comprises:

[0018] (a) from 0.1 to 10 mg/ml of buprenorphine

- [0019] (b) from 0.1 to 20 mg/ml of a chitosan, and
- [0020] (c) from 50 to 200 mg/ml of a polyoxyethylene-polyoxypropylene copolymer of the general formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$ wherein a is from 2 to 130 and b is from 15 to 67;
- [0021] which solution has a pH of from 3 to 4.8.
- [0022] A preferred solution of the invention has a pH of from 3.5 to 4.0, is substantially free from divalent metal ions and comprises:
- [0023] (a) from 1 to 6 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof, calculated as buprenorphine,
- [0024] (b) from 10 to 40 mg/ml of a pectin which has a degree of esterification from 10 to 35%, and
- [0025] (c) dextrose as a tonicity adjustment agent.
- [0026] The invention also provides:
- [0027] a process for the preparation of solution (1), which comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof in water; mixing the resulting solution with a solution in water of a pectin having a degree of esterification of less than 50% such that the mixed solution comprises from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof and from 5 to 40 mg/ml of the pectin; and adjusting the pH of the solution to a value from 3 to 4.2 if desired;
- [0028] a process for the preparation of solution (2), which comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof, a chitosan and HPMC in water to provide a solution comprising from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof, from 0.1 to 20 mg/ml of chitosan and from 0.1 to 15 mg/ml of HPMC; and adjusting the pH of the solution to a value from 3 to 4.8 as desired;
- [0029] a process for the preparation of solution (3), which comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof, a chitosan and a polyoxyethylene-polyoxypropylene copolymer of the general formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$ wherein a is from 2 to 130 and b is from 15 to 67, in water to provide a solution comprising from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof, from 0.1 to 20 mg/ml of a chitosan and from 50 to 200 mg/ml of the polyoxyethylene-polyoxypropylene copolymer; and adjusting the pH of the solution to a value from 3 to 4.8 as desired;
- [0030] a nasal delivery device loaded with a solution of the invention;
- [0031] use of a solution of the invention for the manufacture of a nasal delivery device for use in inducing analgesia; and
- [0032] a method of inducing analgesia in a patient in need thereof, which method comprises intranasally
- [0033] The invention enables a therapeutic blood plasma concentration of buprenorphine, i.e. a buprenorphine concentration that produces pain relief or pain amelioration, to be attained within 30 minutes and maintained for up to 24 hours. The term C_{ther} denotes a therapeutic blood plasma concentration. The term T_{maint} denotes the duration for which C_{ther} is maintained.
- [0034] Additionally, therefore, the present invention provides use of buprenorphine or a physiologically acceptable salt or ester thereof and a delivery agent for the manufacture of a medicament for administration intranasally for the treatment of pain whereby, on introduction into the nasal cavity of a patient to be treated, the buprenorphine or salt or ester thereof is delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration C_{ther} of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours. Also provided are:
- [0035] use of a pharmaceutical composition which comprises buprenorphine or a physiologically acceptable salt or ester thereof and a delivery agent for the manufacture of a nasal delivery device for use in inducing analgesia whereby, on introduction into the nasal cavity of a patient to be treated, the buprenorphine or salt or ester thereof is delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration C_{ther} of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours;
- [0036] a pharmaceutical composition suitable for use as an analgesic which comprises buprenorphine or a physiologically acceptable salt or ester thereof and a delivery agent whereby, on introduction into the nasal cavity of a patient to be treated, the buprenorphine or salt or ester thereof is delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration C_{ther} of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours;
- [0037] a method of inducing analgesia in a patient in need thereof, which method comprises administering intranasally to said patient a pharmaceutical composition which comprises buprenorphine or a physiologically acceptable salt or ester thereof and a delivery agent whereby, on introduction into the nasal cavity of said patient to be treated, the buprenorphine or salt or ester thereof is delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration C_{ther} of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours.

BRIEF DESCRIPTION OF DRAWINGS

[0038] FIGS. 1 to 3 show the pharmacokinetic profiles that were obtained when buprenorphine formulations according to the invention (Formulations A to C) were administered intranasally to healthy volunteers at a dose of 800 μg of buprenorphine hydrochloride, calculated as buprenorphine. Formulation A: buprenorphine hydrochloride-pectin solution. Formulation B: buprenorphine hydrochloride-chitosan/hydroxypropylmethylcellulose (HPMC) solution. Formula-

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