SOLID DOSAGE FORMULATIONS OF NARCOTIC DRUGS HAVING IMPROVED BUCCAL ADSORPTION

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<table>
<thead>
<tr>
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</thead>
<tbody>
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</tr>
</tbody>
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ABSTRACT

The present invention provides solid dosage formulations of narcotic drugs with improved buccal adsorption. These improved characteristics are provided by the combination of the narcotic drug with an additional non-toxic soluble organic compound. The soluble organic compound contains a primary, secondary or tertiary amine group. The addition of this organic compound favorably alters the kinetics of mucosal penetration such that mucosal penetration times are decreased. This provides for a faster onset of action of the drug.
SOLID DOSAGE FORMULATIONS OF NARCOTIC DRUGS HAVING IMPROVED BUCCAL ADSORPTION

[0001] The present invention concerns solid dosage formulations of narcotic drugs having improved buccal adsorption.

[0002] The formulations of the invention are characterized by the introduction in a buccal formulation of a soluble organic compound having a primary, secondary or tertiary amine group.

BACKGROUND OF THE INVENTION

[0003] Buccal formulations are more and more popular for drug administrations. They exhibit in fact several advantages in comparison with other solid dosage forms; in particular, buccal formulations dissolve in the oral cavity without requiring water for ingestion, allowing the buccal adsorption of drugs coming into contact with the oral mucosa in dissolved form. Sometimes, buccal administration does not unfortunately always allow to obtain a fast onset of action of the drug, as the result of difficulties of the drug to cross the skin barrier of mucosa and to penetrate into the blood stream.

DESCRIPTION OF THE INVENTION

[0004] Surprisingly, it has been found that adding a non-toxic amine to a buccal formulation, the penetration capacity of drugs is significantly improved, allowing to reach an higher and earlier blood concentration of drugs in comparison with formulations without amines.

[0005] The amount of amine required in the formulation ranges between 0.1 to 500% of the moles of active component(s), more preferably 0.5 to 300% and most preferably 1 to 200%.

[0006] Examples of amines used in order to improve bioavailability according to the invention include Histidine, Arginine, Lysine, Triethanolamine, Trimethylamine, Betaine, Pyrrolidine, Guanidine, Cysteamine, Taurine and derivatives and analogues thereof. Arginine is a preferred non-toxic amine.

[0007] Examples of active components that may be advantageously formulated in solid dosage form according to the invention include:


[0009] The invention is illustrated by the following Examples:

EXAMPLE #1

Example #1A

[0010] Preparation of a Oral Dispersible Tablet Containing Amine (Arginine)

[0011] Oral dispersible tablets containing 200 mcg of Fentanyl were obtained as follows:

- A) 1.05 g of Fentanyl and 50 g of PEG 600 were dissolved into 90 g of purified water.

Example #1B

[0016] Preparation of an Oral Dispersible Tablet without Amine (Arginine)

[0017] Oral dispersible tablets containing 400 mcg of Fentanyl have been obtained as follows:

- E) 2.1 g of Fentanyl and 50 g of PEG 600 was dissolved into 90 g of purified water.

[0018] F) 455.62 g of Sorbitol, 455.62 g of Mannitol, 26.67 g of aspartame and 10 g of Citric acid, were granulated together with a water solution containing PEG and Fentanyl citrate.

Despite the dose of Fentanyl administered in the tablets described in example # 1A (200 mcg) is 50% of the dose described in example #1B (400 mcg), the pharmacokinetic parameters are similar, demonstrating a dramatic improvement of the Fentanyl bioavailability for the formulation of the invention.

1. Solid dosage formulations of narcotic drugs in form of buccal tablets characterized by containing a non toxic amine.
2. Formulations according to claim 1, wherein the non-toxic amine is selected from Histidine, Arginine, Lysine, Triethanolamine, Trimethylamine, Betaine, Pyrrolidine, Guanidine, Cysteamine, Taurine and derivatives and analogues thereof.
3. Formulations according to claim 2 wherein the non-toxic amine is arginine.
4. Formulations according to claim 1 wherein the non-toxic amine is present in amounts ranging between 0.1 to 500% of the moles of active component(s), more preferably 0.5 to 300% and most preferably 1 to 200%.

5. Formulations according to claim 1 wherein the narcotic drug is selected from Alfentanil, Buprenorphine, Butorphanol, Codeine, Diphenoxylate, Fentanyl, Heroin, Hydrocodone, Hydromorphone, Oxymorphone, Levorphanol, Levallorphan, Loperamide, Meperidine, Morfine, Nalbuphine, Nalmefene, Nalorphine, Naloxone, Naltrexone, Remifentanil, Sufentanil.

6. Formulations according to claim 5 wherein the active ingredient is Fentanyl.

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