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(54) Titre : FORMULATIONS POSOLOGIQUES SOLIDES DE MEDICAMENTS NARCOTIQUES PRESENTANT UNE ADSORPTION BUCCALE AMELIOREE

(54) Title: SOLID DOSAGE FORMULATIONS OF NARCOTIC DRUGS HAVING IMPROVED BUCCAL ADSORPTION

(57) Abrégé/Abstract:
Disclosed is a pharmaceutical composition in the form of a tablet suitable for dissolution in the buccal cavity, said composition comprising i) an effective amount of a narcotic active ingredient, and ii) a pharmaceutically acceptable amine having a pK of about 8 or greater, wherein the molar ratio of amine:active ingredient is from about 5:1 to about 1000:1.

ABSTRACT

Disclosed is a pharmaceutical composition in the form of a tablet suitable for dissolution in the buccal cavity, said composition comprising i) an effective amount of a narcotic active ingredient, and ii) a pharmaceutically acceptable amine having a pK of about 8 or greater, wherein the molar ratio of amine:active ingredient is from about 5:1 to about 1000:1.

SOLID DOSAGE FORMULATIONS OF NARCOTIC DRUGS HAVING IMPROVED BUCCAL ADSORPTION

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

The formulations of the invention are characterized by the introduction in a buccal formulation of a pharmaceutically acceptable soluble organic compound having a primary, secondary or tertiary amine group, having a pK of about 8 or greater. Preferably, the *in vivo* disintegration time of tablets occurs in a time between about 5 and about 25 minutes.

Background of the invention

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

Surprisingly, it has been found that adding a non-toxic or pharmaceutically acceptable amine to a buccal formulation, the penetration capacity of drugs is significantly improved, allowing to reach a higher and earlier blood concentration of the active ingredient in comparison with formulations without an amine as described herein.

The invention provides in one particular embodiment a pharmaceutical composition in the form of a tablet suitable for dissolution in the buccal cavity, said composition comprising i) a pharmaceutically effective amount of a narcotic active ingredient, and ii) a pharmaceutically acceptable amine having a pK of about 8 or greater, wherein the molar ratio of amine:active ingredient is at least about 5:1.

Non-toxic amines having a pK of about 8 or greater which improve the bioavailability according to the invention belong to the following categories:

- basic amino acids, such as Arginine, Lysine, Histidine, and Ornithine;

- tertiary amines, such as Triethanolamine, and Thromethamine;

- aminosulfonic acids, such as Taurine;

- mercapramines such as Cysteamine;

- quaternary ammonium salts, such as Betaine;

- heterocyclic amines, such as Pyrrolidine; and

- Guanidines.

Arginine is a preferred non-toxic amine. The formulations of the invention may include a mixture of two or more of said amines. Preferably, the amine is not polyvinylpyrrolidone.

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

Alfentanil, Buprenorphine, Butorphanol, Codeine, Diphenoxylate, Fentanyl, Heroin, Hydrocodone, Hydromorphone, Oxymorphone, Levophanol, Levallorphan, Loperamide, Meperidine, Morphine, Nalbuphine, Nalmefene, Nalorphine, Naloxone, Naltrexone, Remifentanyl, Sufentanyl and derivatives, salts and analogues thereof. Fentanyl is preferred. The invention further includes the use of pharmaceutically acceptable forms of the active ingredient, such as salts, hydrates, etc., for example, Fentanyl citrate.

Preferably, the amount of amine in respect to the active ingredient (molar ratio amine:active ingredient) ranges from about 5:1 to about 1000:1, preferably from about 10:1 to about 500:1, and most preferably from about 20:1 to about 250:1.

Preferably, the disintegration time *in vivo* ranges between about 2 and about 50 minutes, more preferably between about 5 and about 25 minutes.

It will be understood that the present formulations may additionally contain ingredients typically found in tablets intended for buccal administration, such as one or more of diluents, binders, lubricants, glidants, disintegrants, coloring agents, flavouring agents, etc. The tablets may be made

by conventional techniques, including wet, dry or fluid-bed granulation methods, or direct compression. Preferably, the tablets are not lyophilized.

The invention is illustrated by the following non-limiting Examples:

Example #1

Example #1A

Preparation of an oral dispersible tablet containing amine (Arginine)

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

A) 1.05 g of Fentanyl citrate and 50 g of PEG 6000 were dissolved into 90 g of purified water.

B) 335.62 g of Sorbitol, 516.67 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.

C) At the end of granulation and drying, 43.33 g of arginine free base and 16.67 g of magnesium stearate were added.

D) The product was blended until homogeneity and compressed in toroidal tablets having a diameter of 10 mm and weighing 300 mg each and having hardness of about 70 Newton.

Comparative Example #1B

Preparation of an oral dispersable tablet without amine

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

E) 2.1 g of Fentanyl citrate and 50 g of PEG 6000 were dissolved into 90 g of purified water.

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.

G) The product was blended until homogeneity and compressed in

toroidal tablets having a diameter of 10 mm and weighing 300 mg each having hardness of tablets of 30 Newton.

Example # 2

A pharmacokinetic study was carried out on 6 fasting healthy volunteers treated with a buccal formulation prepared in accordance with example # 1A containing 200 mcg of Fentanyl. The results were compared with a pharmacokinetic study carried out on 6 healthy volunteers treated with a buccal formulation prepared in accordance with example # 1B containing 400 mcg of Fentanyl.

The results are reported in the following Table 1:

	Fentanyl strength per dosage	Disintegration Time *in vivo*	T max	C max	AUC
Example # 1A	200 mcg	15 minutes	48 minutes	496 pg/ml	2430 h*(pg/ml)
Example # 1B	400 mcg	5 minutes	35 minutes	491 pg/ml	3331 h*(pg/ml)

Despite the dose of Fentanyl administered in the tablets described in example # 1A (200 mcg) being 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.

Example # 3

A pharmacokinetic study was carried out on 6 fasting healthy volunteers treated with a buccal formulation prepared in accordance with example # 1A containing 200 mcg of Fentanyl. The results were compared with a pharmacokinetic study carried out on 6 healthy volunteers treated with a buccal formulation commercially available (Actiq™-commercialized by Cephalon, Inc., Salt Lake City, UT 84116 USA) containing 200 mcg of Fentanyl.

The results are reported in the following Table 2:

	Fentanyl strength per dosage	Disintegration Time *in vivo*	Tmax	Cmax	AUC
Example # 1A	200 mcg	15 minutes	48 minutes	496 pg/ml	2430 h*(pg/ml)
Actiq	200 mcg	15 minutes	3.25 hours	237 pg/ml	1607 h*(pg/ml)

Despite the dose of Fentanyl administered in the tablets described in example # 1A (200 mcg) being equal to the dose of Actiq (200 mcg), the pharmacokinetic parameters are much higher, demonstrating a dramatic improvement of the Fentanyl bioavailability for the formulation of the invention.

CLAIMS

1. A pharmaceutical composition in the form of a tablet suitable for dissolution in the buccal cavity, said composition comprising

i) a pharmaceutically effective amount of a narcotic active ingredient, and

ii) a pharmaceutically acceptable amine having a pK of about 8 or greater,

wherein the molar ratio of amine:active ingredient is at least about 5:1.

2. The composition according to claim 1, wherein the amine is a basic amino acid, a tertiary amine, an aminosulfonic acid, a mercapramine, a quaternary ammonium salt, a heterocyclic amine, or a guanidine, or mixtures thereof.

3. The composition according to claim 2, wherein the amine is Arginine, Lysine, Histidine, Triethanolamine, Thromethamine, Taurine, Cysteamine, Betaine, Guanidine, or Pyrrolidine, or mixtures thereof.

4. The composition according to claim 3, wherein the amine comprises Arginine.

5. The composition according to claim 1, wherein the narcotic active ingredient is Alfentanyl, Buprenorfine, Butorphanol, Codeine, Diphenoxylate, Fentanyl, Heroin, Hydrocodone, Hydromorphone, Oxymorphone, Levophanol, Levallorphan, Loperamide, Meperidine, Morphine, Nalbuphine, Nalmefene, Nalorphine, Naloxone, Naltrexone, Remifentanyl, or Sufentanyl, or pharmaceutically acceptable salts, hydrates or mixtures thereof.

6. The composition according to claim 5, wherein the active ingredient is Fentanyl or a pharmaceutically acceptable salt thereof.

7. The composition according to claim 1, wherein the molar ratio of amine:active ingredient is from about 5:1 to about 1000:1.

8. The composition according to claim 7, wherein the molar ratio of amine:active ingredient ranges from about 10:1 to about 500:1.

9. The composition according to claim 8, wherein the molar ratio of amine:active ingredient ranges from about 20:1 to about 250:1.

10. The composition according to claim 5, wherein the tablet has a disintegration time *in vivo* of about 2 to about 50 minutes.

11. The composition according to claim 10, wherein the tablet has a disintegration time *in vivo* of about 5 to about 25 minutes.

12. A pharmaceutical composition in the form of a tablet suitable for dissolution in the buccal cavity, said composition comprising

i) a pharmaceutically effective amount of a narcotic active ingredient comprising Fentanyl or a pharmaceutically acceptable salt thereof, and

ii) arginine,

wherein the molar ratio of arginine:active ingredient is at least about 5:1.

13. Use of a pharmaceutical composition in the form of a tablet suitable for dissolution in the buccal cavity, said composition comprising

i) a pharmaceutically effective amount of a narcotic active ingredient, and

ii) a pharmaceutically acceptable amine having a pK of about 8 or greater,

wherein the molar ratio of amine:narcotic active ingredient is at least about 5:1 for administration of the narcotic active ingredient to a mammal across the oral mucosa thereof.

14. The use according to claim 13, wherein the active ingredient comprises Fentanyl or a pharmaceutically acceptable salt thereof, and the amine comprises arginine.