OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

(12) (19) (CA) **Demande-Application**

(21) (A1) **2,336,706**

(86) 1999/07/27
(87) 2000/02/10

(72) BOERJAN, WOUT, BE
(72) CHEN, CUIYING, BE
(71) VLAAMS INTERUNIVERSITAIR INSTITUUT VOOR BIOTECHNOLOGIE VZW, BE

(51) Int.Cl.[7] C12N 15/82
(30) 1998/07/27 (98202518.1) EP

(54) **PROMOTEUR DE VEGETAL INDUIT PAR FLEXION OU INCLINAISON**

(54) **BENDING AND/OR LEANING-INDUCED PLANT PROMOTER**

(57) The present invention concerns the use of a promoter with SEQ.ID.NO.1 or with SEQ.ID.NO.2 or a functional fragment thereof, to obtain induction of gene expression by several kinds of mechanical stress, such as bending, elongation, compression, leaning, agitation or gravity and the like.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 9/20, 31/19, 31/195

A1

(11) International Publication Number: **WO 00/06125**

(43) International Publication Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/EP99/04874

(22) International Filing Date: 12 July 1999 (12.07.99)

(30) Priority Data:
MI98A001774 30 July 1998 (30.07.98) IT

(71) Applicant: ZAMBON GROUP S.P.A. [IT/IT]; Via della Chimica, 9, I–36100 Vicenza (IT).

(72) Inventors: GRASSANO, Alessandro; Via Volturno, 21, I–20052 Monza (IT). MARCHIORRI, Maurizio; Via Don Orsenigo, 11, I–22039 Valbrona (IT). DI TORO, Mauro; Via Vittorino Mandelli, 18/A, I–20050 Ronco Briantino (IT). CASTEGINI, Franco; Strada Gogna, 37, I–36100 Vicenza (IT).

(74) Agent: LONGONI, Alessandra; Zambon Group S.p.A., Corp. Patent & Trademark Dept., Via Lillo del Duca, 10, I–20091 Bresso (IT).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: FAST DISSOLVING IBUPROFEN CONTAINING COMPOSITIONS HAVING ANALGESIC ACTIVITY

(57) Abstract

An analgesic composition useful in the preparation of fast dissolving tablets is provided wherein the composition is the result of combining ibuprofen, arginine, linear PVP and an alkaline bicarbonate to which usual excipients for the preparation of tablet are added.

FAST DISSOLVING IBUPROFEN CONTAINING COMPOSITIONS HAVING ANALGESIC ACTIVITY

****

The present invention relates to an analgesic composition for preparing fast dissolving tablets containing ibuprofen and arginine and the tablets made therefrom.

Ibuprofen is the International common name of the compound 2-(4-isobutylphenyl)-propionic acid, which is a known drug with analgesic, as well as anti-inflammatory and antipyretic, activity of broad diffusion.

In U.S. Patent No. 4,279,926 (SPA-Società Prodotti Antibiotici S.p.A.) ibuprofen salts with basic amino acids such as arginine and lysine have been described. To our knowledge only the lysine salt has been commercialised.

In U.S. Patent No. 4,689,218 (Zambon Group S.p.A.) effervescent compositions of ibuprofen containing arginine together with 20-30% by weight of bicarbonate and 25-40% by weight of sodium bitartrate have been described.

The described formulations are useful for preparing drinkable aqueous solutions.

In U.S. Patent No. 4,834,966 (Zambon Group S.p.A.) non-effervescent compositions are disclosed consisting, as a base, of a ternary mixture consisting of ibuprofen, 1.1 to 1.5 mol% arginine per mole of ibuprofen and sodium bicarbonate in a weight amount between 0.25 and 0.75 times the weight of ibuprofen.

These formulations are disclosed as very suitable for the preparation of granulates quickly soluble in water.

The administration of the so obtained aqueous solutions assures a fast analgesic effect which is achieved in about ten minutes.

Sachets containing the granulate of US 4,834,966 are on the market.

In some Countries, and in particular in the U.S.A., the preparations in the form of a sachet are not particularly appreciated by the public, who generally prefer the use of tablets in the treatment of conditions which need an analgesic drug.

The commercially available tablets containing ibuprofen do not have a particularly fast effect because they require about 30 minutes to completely dissolve and reach the blood stream.

In order to obtain a quick dissolution of the active principle, the present inventors tried preparing tablets starting from the ibuprofen-arginine-sodium bicarbonate ternary mixture of

the above mentioned U.S. Patent No. 4,834,966.

Unfortunately, it was impossible to obtain satisfactory results because the resulting tablets were too friable and subject to fragmentation during manufacturing and packaging.

Therefore, there was the problem to have available tablets having good workability and a fast dissolution so as to assure a prompt analgesic effect.

These results have been obtained thanks to a new mixture containing ibuprofen, arginine, linear polyvinylpyrrolidone (PVP) and a reduced amount of an alkaline bicarbonate.

Therefore, an object of the present invention is an analgesic composition comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen.

A further object of the present invention is a fast dissolution tablet comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen and including also normal excipients useful for the preparation of tablets.

Preferably ibuprofen is contained in amounts of from 100 to 400 mg/tablet, more preferably in amounts of 100, 200 mg/tablet, most preferably in an amount of 200 mg/tablet.

Arginine is preferably contained in an n amount from 1.1 to 1.3 moles per mole of ibuprofen and more preferably in an amount of 1.2 moles per mole of ibuprofen.

Linear PVP is preferably a PVP having an average K value, determined according to the method described in the U.S. Pharmacopoeia XXIII, of from 25 to 90, more preferably from 50 to 90, most preferably PVP K90. It is preferably used in an amount of from 2 to 8% by weight with respect to the weight of ibuprofen.

The alkaline bicarbonate is sodium and potassium bicarbonate and it is preferably used in an amount of from 7 to 10% by weight with respect to the weight of ibuprofen.

Within the present context the identity of the components and amounts thereof refer to the weight and identity of the starting materials used in preparing the composition. It is possible that during preparation of the composition and/or tablets, some interaction or reaction may

occur between two or more components. To the extent that such interaction or reaction occurs the present invention is intended to cover such occurrences.

Normal excipients useful in the preparation of the tablets include, but are not limited to: lubricants such as magnesium stearate, sodium stearyl fumarate and sodium benzoate; anti-adherents such as talc and polyethylenglycol; glidants such as colloidal silica; diluents such as dicalcium phosphate, cellulose (for example microcrystalline cellulose) and its derivative, carbohydrates and polyalcohols such as saccharose, xylitol and lactose; disintegrants such as reticulate vinylic polymers (such as crosslinked PVP), derivatives of starch and of cellulose such as sodium carboxymethyl-starch and sodium croscarmelose; wetting agents such as TWEEN 80 (Trademark registered by ICI of Americas for polysorbate) and sodium lauryl sulphate.

Suitable excipients and their amounts can be readily determined by the man skilled in the art according to the methods normally used in pharmaceutical technology. However, in the present invention, it is important to avoid excipients that would cause a significant decrease in tablet dissolution rate. Further, excipients must allow a good workability of the tablet.

In preparing the tablet of the present invention it is preferable to prepare a granulate with the mixture of ibuprofen, arginine and linear PVP, to mix to it the bicarbonate and the excipients, and then to compress.

When desired, the tablets can be film coated with a coating readily soluble in the gastric environment.

Suitable coatings can be prepared using conventional tablet coating compositions and methods. Preferred coatings include OPADRY II (sold by Colorcon; a mixture of hydroxypropyl methyl cellulose, pigments and a plasticizer), EUDRAGIT (sold by Rohm Pharma; a methacrylic acid ester polymer) and a combination of OPADRY II with saccharose.

The granulate can be prepared by direct granulation of the three components (ibuprofen, arginine and liner PVP) in the desired amounts or, after a first granulation of arginine with melted ibuprofen, by granulating a second time with linear PVP.

Both granulates obtained according the above described methods are then screened, dried,

combined with bicarbonate and any selected excipient(s) in the desired amounts and compressed in suitable moulds for obtaining the desired tablets which can then be film coated, if desired.

In addition to good handling and good workability, the tablets of the present invention provide complete dissolution of the active ingredient in about 10 minutes or less. Consequently the release is faster with respect to the commercially available ibuprofen based analgesic tablets (see example 5).

Generally, linear PVP is considered a binder at the amounts used in the present invention, and would be thus expected to inhibit dissolution or have little or no effect on dissolution.

With the aim to better illustrate the present invention the following examples are now given.

Example 1

Method for the preparation of the granulate of ibuprofen, arginine and linear PVP

Into an Erweka planetary mixer equipped with a thermostatic jacket bowl the entire quantity of ibuprofen was charged and melted at a temperature of 80°C under continuous stirring.

After all ibuprofen was entered, arginine, PVP and boiling water were added in that order.

After about 10 minutes of continuos stirring a creamy mass was obtained which was slowly cooled down to room temperature thus obtaining a solid granular mass.

Drying was completed by placing the granulate in a whirlpool static oven regulated at a temperature of 45°C for about 15 hours.

An alternative procedure involved preparing the ibuprofen and arginine granulate, to which powdered linear PVP was added and a second granulation of the mixture with cold water was carried out. The wet granulate obtained was dried in a whirlpool static oven. The alkaline bicarbonate and the excipients were then added.

Example 2

Alternative method for the preparation of ibuprofen, arginine and linear PVP granulate

Into a fast granulator water and arginine were sequentially introduced. When the arginine was partially dissolved, ibuprofen and linear PVP were added in sequence, and the mixture warmed under continuous stirring for about 30 minutes to obtain a creamy mass.

The creamy mass was then dried under vacuum for about 50 minutes.

At the end of drying the obtained mass was screened through an oscillating granulator equipped with a 1.5 mm sieve.

To the obtained granulate, bicarbonate and the excipients were then added.

The above described granulation method was also used in the preparation of an ibuprofen-arginine granulate to which powdered linear PVP was subsequently added.

The resulting mixture was granulated with cold water and the wet granulated product was dried in a static oven or directly into the granulator. The bicarbonate and the excipients were then added.

Example 3

Preparation of tablets

The granulate containing ibuprofen-arginine and linear PVP, obtained according to the procedure described in the example 1 or in the example 2, and to which bicarbonate and the excipients were added, was compressed to the desired weight.

Example 4

By operating according to the procedure described in the example 3, the tablets whose composition is reported in the following table 1 were prepared.

Table 1

Compositions according to the invention

Ingredients	Tablets (mg)						
	A	B	C	D	E	F	G
Ibuprofen	200	200	200	200	200	400	400
Arginine	185	185	185	185	185	370	370
PVP K90	5.4	5.4	5.4	5.4	5.4	10.8	10.8
Sodium bicarbonate	20	20	20	15	20	40	40
Microcrystalline cellulose	156			156	141	103	
Lactose		156					103
Dicalcium phosphate			156				
Sodium croscarmelose				30			
Sodium carboxymethyl starch			30				50
Reticulate PVP	30	30			30	50	
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	5.0	5.0
Colloidal silica	0.6	0.6	0.6	0.6	0.6	1.2	1.2
Tablet total weight (mg)	600	600	600	600	600	980	980

Example 5

Determination of the dissolution rate of tablets of the present invention

Determination of the dissolution rate was carried out by applying the method described in the U.S. Pharmacopeia XXIII, NF XVII, supplement No. 5.

Into a dissolution bath a solution of pH 7.2 phosphate buffer was charged and the liquid was thermostated at a temperature of 37°C.

The tablet to be checked was then charged and under continuous stirring by paddle at 50 rpm, the amount of ibuprofen in solution, expressed in percentage released as a function of time, was measured.

The tablets of the invention had an excellent dissolution rate in comparison with commercially available tablets containing the same amount of ibuprofen.

As an example, the ibuprofen contained in tablet A (see table 1) was completely in solution in 10 minutes according to the above described test, while a tablet of MOTRIN® (Upjohn) and one of ANTALGIL® (Jannsen-Cilag), containing the same amount of ibuprofen of tablet A, showed the release of a percentage of ibuprofen in solution of about 45% and 65% respectively, after 10 minutes.

It was necessary to wait at least 30 minutes before observing complete dissolution of the ibuprofen contained in the MOTRIN® and ANTALGIN® tablets.

Claims

1) An analgesic composition comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen.

2) A fast dissolving tablet comprising ibuprofen; from 1.1 to 1.5 moles of arginine per mole of ibuprofen; from 0.5 to 10% by weight of linear PVP with respect to the weight of ibuprofen; and from 5 to 10% by weight of an alkaline bicarbonate respect to the weight of ibuprofen and including also normal excipients useful for the preparation of tablets.

3) A tablet according to claim 2, wherein the ibuprofen is present in an amount of from 100 to 400 mg.

4) A tablet according to claim 2, wherein the ibuprofen is present in an amount of from 200 to 400 mg.

5) A tablet according to claim 2, wherein arginine is present in an amount of from 1.1 to 1.3 moles per mole of ibuprofen.

6) A tablet according to claim 5, wherein the arginine:ibuprofen molar ratio is 1.2:1.

7) A tablet according to claim 2, wherein the linear PVP has an average K value of from 25 to 90.

8) A tablet according to claim 7, wherein the linear PVP is PVP K90.

9) A tablet according to claim 2, wherein the alkaline bicarbonate is sodium or potassium bicarbonate.

10) A tablet according to claim 2, wherein ibuprofen is present in an amount of 200 or 400 mg, arginine is present in an amount of 1.2 moles per mole of ibuprofen, the linear PVP is PVP K90 and the alkaline bicarbonate is sodium bicarbonate.