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(54) Title: ANALGESICAL ORAL COMPOSITION WITH CONTROLLED RELEASE OF AN OPIOID

(57) Abstract: The invention discloses the formulation and method of the preparation of a solid oral therapeutic composition with controlled release of the active substance, which contains dihydrocodeine and its pharmaceutically acceptable salts in a required quantity together with micronized ester of glycerol with behenic acid, calcium phosphate dihydrate, a copolymer of vinylpyrrolidone and vinylacetate and with the sodium salt of the ester of fumaric acid and stearyl alcohol.

ANALGESICAL ORAL COMPOSITION WITH CONTROLLED RELEASE OF AN OPIOID

Technical Field

The invention falls under the area of pharmacy and it addresses a composition and a method for preparing a therapeutic formulation containing, as the active substance, dihydrocodeine and/or its pharmaceutically acceptable salts in the form of tablets with controlled release of this active substance that belongs to the therapeutic group of strongly potent analgesics.

State of the Art

A composition and a method of manufacturing an oral composition with controlled release of dihydrocodeine tartrate is illustrated in EP 0 249 347 owned by Euroceltique SA. The product is a matrix tablet containing, in addition to the active substance, also suitable matrix-forming materials that provide for gradual release of dihydrocodeine tartrate, mass equivalents of dihydrocodeine base or other dihydrocodeine salts.

Preferably used are hydroxyethyl cellulose, cetostearyl alcohol, anhydrous lactose, talc and magnesium stearate.

The manufacturing principle is the granulation of the active substance in admixture with lactose and hydroxyethyl cellulose and water, drying out of the granulate, followed by adding of melted cetostearyl alcohol at an elevated temperature. After mixing up, followed by cooling the mixture down with air, re-granulating and sieving the granulate, talc and magnesium stearate is added. Tablets are compressed out from this mixture.

An disadvantage of the above specification is the use of two materials forming the matrix for gradual release of the active substance. These are hydroxyethyl cellulose and cetostearyl alcohol. The key disadvantage is the need to perform the basic technological operation when hot, which requires a granulation device having the possibility of heating of the processed material and a need of use of melted cetostearyl alcohol which, in the course of intensive stirring, forms a coat on the particles of the granulate of the active substance, lactose and hydroxylethyl cellulose. After the mixture is cooled down, properly treated and compressed into tablets, the required course of release of the active substance from the therapeutic formulation prepared in the above-described manner is achieved.

Substance of the Invention

The above described disadvantages are addressed in this invention, according to which oral tablets with controlled release containing a therapeutic dose of dihydrocodeine and/or an equivalent amount of other therapeutically acceptable dihydrocodeine salts are prepared using a new, simpler and less demanding technological process that does not require any special manufacturing device for the granulation with a supply of heat energy and without any need of incorporating auxiliary materials influencing release of the therapeutic agent in the molten state.

The required profile of release of the active substance after compressing into tablets is achieved by using a single adjuvant responsible for the required effect and a pharmaceutical water-insoluble filler, by their mutual weight combination, or by disintegrating a portion of the pressings through a sieve having a proper mesh size and mixing the disintegrate with the primary mixture in an experimentally verified ratio.

The oral tablets prepared using the method of the invention comply with the requirements for the release and they do not need any additional treatment such as coating with a film. They can be divided by a line to facilitate possible breaking into smaller doses without any impact of the tablet breaking upon the course of released of the active substance used.

Another advantage of the below described invention is the possibility of processing of the mixture into pressings having any required therapeutic content of the active substance and any shape, the release profile being maintained.

The principle of the manufacture is simple mixing of the active substance with adjuvants, moistening of the mixture during stirring until formation of the required structure of the granulate, its drying and proper sizing of the particles of the granulate, addition of a lubricant facilitating the compressing process and forming of tablets of required weight, shape and fracture resistance that are chemically and physically stable for a sufficient period of time and can be inserted into commonly used pharmaceutical packages without problems.

The analgesically active oral therapeutic composition with controlled release of an opioid active substance and the method for its preparation according to this invention comprise, in addition to dihydrocodeine tatrate and/ or dihydrocodeine base and/or pharmaceutically salts of dihydrocodeine, other adjuvants suitable for pharmaceutical formulations, namely:

a) Micronized esters of glycerol and higher fatty acids, preferably the glyceryl ester of behenic acid, having the particle size ranging from 1 to 100 μm, preferably having such particle size distribution that 90 % of them is sized from 1.5 to 60 μm.

It has been found out experimentally and verified that the most beneficial content of the glyceryl esters of higher fatty acids, preferably using the glyceryl ester of behenic acid, to achieve the required properties of the therapeutic composition according to this invention is from 10 to 65 % by weight, preferably from 20 to 50 % by weight of the tablet.

b) Pharmaceutically applicable alkali salts of phosphoric acid, preferably calcium phosphate dihydrate, in an amount from 10 to 60 % by weight, preferably from 15 % to 50 % by weight of the tablet.

c) A copolymer of vinylpyrrolidone and vinylacetate in the ratio of 6 : 4, having the relative molecular weight from 45,000 to 70,000, in an amount from 1.0 to 6 % by weight, preferably from 1.5 % to 4,0 % by weight.

d) A micronized alkali salt of fumaric acid and stearyl alcohol, preferably the sodium salt of the ester of fumaric acid and stearyl alcohol, having the particle size up to10 μm, preferably up to 8 μm, in an amount from 0.2 to 3 % by weight, preferably from 0.8 to 1,5 % by weight.

It has been surprisingly found out and confirmed that the profile of the release of the active substance from the therapeutic composition according to the described invention can be set as required by modifying the ratio of the glyceryl ester of behenic acid and calcium phosphate dihydrate in the tablet.

It has been further found out and confirmed that by disintegrating the compacts through a properly sized sieve and the re-compressing of the ground material a surprisingly rapid drop in the rate of the release of the active substance is obtained. Combining amounts of the primary mixture for the compression of tablets and of the disintegrated mixture permits to influence the process of release of the active substance from the tablet.

The essence of the manufacture of the solid oral dosage form of this invention resides in mixing, in a high-speed pharmaceutical homogenizer for wet homogenisation, the active substance together with micronized glycerol esters of higher fatty acids, preferably using the glyceryl ester of behenic acid having the particle size from 1.5 to 60 μm, in an amount from 20

to 50 % by weight and with alkali salts of phosphoric acid, preferably using calcium phosphate dihydrate, in an amount from 15 to 50 % by weight. This mixture is gradually moistened with a solution of a vinylpyrrolidone-vinylacetate co-polymer in the ratio 6 : 4 having the relative molecular mass weight from 45,000 to 70,000 in an amount from 1.5 to 4.0 % by weight in a mixture of ethyl alcohol and water wherein ethyl alcohol accounts for 10 to 80 % by volume, preferably from 25 to 70 % by volume. The mixture is shortly stirred until agglomerate is formed.

Thus prepared agglomerate is box dried, or fluidization dried, or vacuum dried, or microwave dried, preferably fluidization dried, such that the final humidity is in the range from 0.1 to 2.0 % by weight, preferably from 0.5 to 1.5 % by weight. The temperature of the product when dried has to reach 35 to 42 °C, preferably 39 to 41 °C.

The dried agglomerate is subjected to resizing of the particles to match the requirements of the tablet compressing process and is homogenized with the micronized sodium salt of the ester of stearyl alcohol with fumaric acid. After thorough homogenisation, the mixture is ready for the tablet compressing process and is compressed in rotary tablet forming machines into tablets having the required contents of the active substance, the fracture resistance of the tablets being from 40 to 110 N, preferably from 60 to 85 N. The tablets may be flat round-shaped, lens round-shaped, of an oval or other shape, with possible presence of a break line on one or two surfaces of the tablet.

Thus obtained tablets can be adjusted into versatile packages destined for pharmaceutical products, preferably into a blister package consisting of a PVC/PVDC combination of heat formed sheet and an aluminium foil coated with an adhesive material.

Examples

The subject-matter of the invention is illustrated in, but not limited by, the following examples.

Example 1

a) Tablet composition

Dihydrocodeine tartrate	33.33 %
Behenic acid glyceryl ester	46.66 %

Calcium phosphate dihydrate	16.39 %
Vinylpyrrolidone-vinylacetate co-polymer	2.51 %
Sodium stearyl fumarate	1.11 %

b) Process of preparing

Dihydrocodeine tartrate is, in a suitable type of a pharmaceutical granulator, blended with micronized glyceryl ester of behenic acid having the particle size from 1 to 60 μm and with calcium phosphate dihydrate. The blended mixture is moistened gradually with a solution of a vinylpyrrolidone-vinylacetate co-polymer in the ratio 6:4 in a mixture of 48 % ethyl alcohol – water until agglomerate forms. The agglomerate is transferred to the vessel of a device for fluidization drying and is dried under moderate fluidization at the temperature of the supplied air 55 ° C until the temperature of the product reaches 40 °C, which at the same time indicates completion of the drying process.

The dried out granulate is subjected to resizing by means of oscillation sieving with a sieve having openings from 0.65 to 0.8 mm and it is homogenized in a dry homogenizer device with a lubricant, namely micronized sodium stearyl fumarate.

At this point, the mixture is ready for compressing in rotary tablet forming machines into tablets having the required contents of dihydrocodeine tartrate and the required fracture resistance.

c) Dissolution test results (USP Paddle Method 900 ml, 100 rpm, aq. buffer pH 1.6-7.2)

1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	7 hours	8 hours
36.90 %	64.60 %		100 %				

Example 2

a) Tablet composition

Dihydrocodeine tartrate	33.33 %
Behenic acid glyceryl ester	16.39 %

Calcium phosphate dihydrate	46.66 %
Vinylpyrrolidone-vinylacetate co-polymer	2.51 %
Sodium stearyl fumarate	1.11 %

b) Process of preparing: same as in ***Example 1***

c) Results of the dissolution test

1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	7 hours	8 hours
47.1 %	62.8 %		83.7 %		92.4 %		93. 6 %

Example 3

a) Tablet composition:

Dihydrocodeine tartrate	30.15 %
Behenic acid glyceryl ester	28.90 %
Calcium phosphate dihydrate	37.69 %
Vinylpyrrolidone-vinylacetate co-polymer	2.26 %
Sodium stearyl fumarate	1.00 %

b) Process of preparing: same as in ***Example 1***

c) Results of the dissolution test:

1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	7 hours	8 hours
37.99 %	53.63 %	64.53 %	72.92 %	79.50 %	84.86 %	89.09 %	92.54 %

Example 4

a) Tablet composition:

Same as in ***Example 1***

b) Process of preparing: same as in ***Example 1***

until the step of compressing the tablets from the finished granulate, of which a 25 % by weight amount is left, the remaining 75 % are compressed into pressings, which are disintegrated by the oscillation method through a sieve having the size of openings from 0.65 mm to 0.80 mm. After the disintegration, both products are homogenized in a homogenizer for dry pharmaceutical homogenising and the resulting product is subjected to the compression process, thus giving tablets that have the required contents of the active substance and the required shape and fracture resistance.

b) Results of the dissolution test:

1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	7 hours	8 hours
32.0 %	45.9 %		65.2 %		79.5 %		94.8 %

Industrial Applicability

The invention may be used in the pharmaceutical industry in the manufacture of therapeutic composition containing gradually released analgesically active therapeutic agent dihydrocodeine and/or its pharmaceutically acceptable salts.

The composition according to this invention is useful in alleviating moderately strong to strong pains, such as post-surgery pains, post-injury pains, chronic pains in the spine, severe arthritis, acute osteoporosis, neurogenic pains, pains related to cancer and other pains.

CLAIMS

1. An analgesically active oral therapeutic composition with controlled release of an opioid active substance, characterized in that it contains a mixture of the active substance and the adjuvants, one of which adjuvants ensuring said controlled release and another adjuvant being a pharmaceutical water-insoluble filler, the release profile of the active substance optionally being set up by the ratio of the disintegrate from the pressings and the primary granulated mixture.

2. The composition according to claim 1 characterized in that the adjuvant ensuring controlled release is a micronized ester of glycerol with higher fatty acids.

3. The composition according to any of claims 1 and 2 characterized in that the water-insoluble filler is at least one pharmaceutically applicable alkali salt of phosphoric acid.

4. The composition according to any of preceding claims characterized in that the active substance is dihydrocodeine and/or its pharmaceutically or therapeutically acceptable salts.

5. The composition according to any of preceding claims characterized in that the contents of the active substance therein is 25 to 40 % by weight, preferably 27 to 35 % by weight.

6. The composition according to claim 2 characterized in that the adjuvant ensuring controlled release is a micronized ester of glycerol with behenic acid.

7. The composition according to claim 3 characterized in that the filler is calcium phosphate dihydrate.

8. The composition according to any of preceding claims characterized in that the adjuvants are calcium phosphate dihydrate in an amount from 10 to 60 % by weight, preferably from 15 to 50 % by weight, the glyceryl ester of behenic acid having the particle size from 1 to 100 μm, preferably such that 90 % of the particles is of a size from 1.5 to 60 μm, and being in an amount from 10 to 60 % by weight, preferably from 20 to 50 % by weight, a copolymer of vinylpyrrolidone and vinylacetate in the ratio 6 : 4 having the relative molecular weight from 45,000 to 70,000 in an amount from 1 to 6 % by weight, preferably from 1.5 to 4 % by weight, and a micronized sodium salt of the ester of fumaric acid with

stearyl alcohol having the particle size up to 10 μm, preferably up to 8 μm, in an amount from 0.2 to 3 % by weight, preferably from 0.8 to 1.5 % by weight.

9. A method for preparing a therapeutic composition characterized in that the active substance is blended in admixture with a micronized ester of glycerol and behenic acid with calcium phosphate dihydrate, during blending the mixture is moistened with a solution of a co-polymer of vinylpyrrolidone and vinylacetate in the ratio 6 : 4 having the relative molecular weight from 45,000 to 70,000 in a mixture of ethyl alcohol and water, thus the mixture being agglomerated.

10. The method according to claim 9 characterized in that the mixture of ethyl alcohol and water, in which the co-polymer of vinylpyrrolidone and vinylacetate is dissolved at the laboratory temperature, consists of 10 to 80 % by volume of ethyl alcohol, preferably 25 to 70 % by weight of ethyl alcohol.

11. The method according to any of claims 9 and 10 characterized in that the agglomerate is box dried, or vacuum dried, or fluidization dried, or microwave dried, preferably fluidization dried, until the residual humidity from 0.1 to 2.0 % by weight, preferably from 0.5 to 1.5 % by weight.

12. The method according to claim 11 characterized in that the temperature of the product during the drying reaches 35 to 42 °C, preferably 39 to 41 °C.

13. The method according to any of claims 9 to 12 characterized in that the dried agglomerate is resized to a particle size to match the tablet compressing process by the oscillation method through a sieve having the size of openings from 0.65 to 0.8 mm, preferably 0.7 mm, a micronised sodium salt of the ester of fumaric acid and stearyl alcohol is admixed in an amount from 0.2 to 3.0 % by weight, preferably 0.8 to 1.5 % by weight, the particle size of which is up to 10 μm, preferably up to 8 μm, and the mixture is compressed into tablets having the required contents of the active substance and having fracture resistance from 40 N to 110 N, preferably form 60 N to 85 N.

14. The method according to any of claims 9 to 12 for preparing the therapeutic composition according to any of claims 1 to 8 characterized in that, in order to achieve the required profile of release of the active substance from the tablet, 1 to 99 % by weight, preferably 65 to 85 % by weight of the finished mixture for compressing is compressed into pressings of

any shape and weight having the fracture resistance from 40 N to 110 N, preferably from 60 N to 85 N, said pressings are disintegrated by the oscillation method through a sieve having the size of openings from 0.65 to 0.8 mm, preferably 0.7 mm, and the disintegrate is thoroughly homogenized with previously not compressed and not disintegrated residue of the prepared lot.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/22 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	page 42 -page 44; example 43	4
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X	WO 01 47497 A (SLOVAKOFARMA) 5 July 2001 (2001-07-05) the whole document	9-14
A	DE 197 47 261 A (BAYER AG) 29 April 1999 (1999-04-29) page 7, line 45 - line 47	9-14
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
14 August 2003	26/08/2003

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 14176 A (GATTEFOSSE S.A.) 9 April 1998 (1998-04-09) page 16 -page 17; example 6 ---	9-14
A	EL-SAYED G M ET AL: "KINETICS OF THEOPHYLLINE RELEASE FROM DIFFERENT TABLET MATRICES" STP PHARMA SCIENCES, PARIS, FR, vol. 6, no. 6, 1 November 1996 (1996-11-01), pages 390-397, XP000676942 ISSN: 1157-1489 page 391, paragraphs 1.,,2. examples F6,,F7 -----	1-14

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