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(71) **Applicant** *(for all designated States except US)*: **ZENTIVA, K.S.** [CZ/CZ]; U Kabelovny 130, 102 37 Praha 10 (CZ).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **SAKOVA, OIga** [SK/SK]; Kopernikova 121, 920 01 Hlohovec (SK). **VLADOVICOVA, Beata** [SK/SK]; Koplotovce 161, 920 01 Hlohovec (SK). **KABZANOVA, Anna** [SK/SK]; Michalska 10, 920 01 Hlohovec (SK). **KORMANOVA, Viera** [SK/SK]; Slnecna 3, 920 01 Hlohovec (SK). **ZORICAK, Stefan** [SK/SK]; Slovenska Ves 202, 059 02 Slovenska Ves (SK).

(74) **Agents**: **JIROTKOVA, Ivana** et al.; ROTT, RUZICKA & GUTTMANN, P.O. Box 44, 120 00 Praha 2 (CZ).

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(54) **Title**: A COMBINED ORAL FORMULATION WITH CONTROLLED RELEASE OF ACETYLSALICYLIC ACID AND A METHOD FOR THE PREPARATION

(57) **Abstract**: A combined oral solid pharmaceutical formulation with controlled release of acetylsalicylic acid, which comprises at least one further active ingredient selected from the group of non-narcotic analgesics and/or natural psychotropic agents, and stearic acid and starch as excipients in a specific ratio, and a method for the preparation thereof.

A combined oral formulation with controlled release of acetylsalicylic acid and a method for the preparation

Technical Field

The invention relates to combined oral formulations with controlled release of acetylsalicylic acid, comprising the active ingredient acetylsalicylic acid, at least one another active ingredient from the group of non-narcotic analgesics and/or natural psychotropic agents, and to a method for the preparation thereof.

Background Art

An oral dosage form, comprising the active ingredients acetylsalicylic acid, paracetamol and caffeine, and a method for the manufacture thereof is described in international application WO 95/07082 A [EGIS Gyógyszergyár RT, HU].

The above-specified tablet comprises the combination of the above-mentioned active ingredients in admixture with pharmaceutical excipients, which are poly(vinyl butyral) as a binder and low-substitution hydroxypropyl cellulose as a disintegrant. The tablets show a satisfactory long-term stability in heavy conditions.

The manufacture described is based on wet granulation of a mixture of the active ingredients acetylsalicylic acid, paracetamol and caffeine. The mixture of the active ingredients is fluid sprayed with a 96% ethanolic solution of poly(vinyl butyral) with stearic acid in the selected ratio. The prepared granulate is fluid dried until a moisture content of the granulate of 0.5%. (The moisture content of the granulate is measured at the conditions of 70°C/30 minutes.) Low-substitution hydroxypropyl cellulose and stearic acid are admixed to the dried and sieved (mesh size 1 mm) granulate. Tablets are compressed from the prepared mixture.

The use of the non-pharmacopeia excipient, poly(vinyl butyral), which is commonly used in the manufacture of glass and plastic materials, is a major drawback of the subject-matter of the above-described patent application. Further drawbacks include the necessity of using the organic solvent (96% ethanol, a flammable liquid); the technology requiring enhanced safety adaptations of the working space and modifications of the manufacturing equipment.

Disclosure of Invention

The above-described drawbacks have been solved by the present invention, in which stable oral tablets with controlled release of acetylsalicylic acid comprise at least one further active ingredient selected from the group consisting of non-narcotic analgesics and natural psychotropic agents, and by a specific ratio of the excipients, preferably of starch and stearic acid, wherein the ratio of acetylic acid to the mixture of stearic acid and starch is preferably from 2:1 to 10:1.

The further active ingredient from the group of non-narcotic analgesics is paracetamol or ibuprofen, the natural psychotropic agent is caffeine.

Suitable starches include corn, potato or rice starch, the corn starch having a moisture content of 3% to 20%, preferably of 11% to 18%. In a preferred embodiment, stearic acid having a particle size of 1 to 20 μm is used; preferably, 90% of stearic acid has a particle size of from 1 to 20 μm. The amount of starch in the formulation is from 2% by weight to 10% by weight, preferably from, 4% by weight to 5% by weight, and the amount of stearic acid is from 1% by weight to 5% by weight, preferably from 1.5% by weight to 3% by weight.

The combined oral formulation, in a preferred embodiment, comprises acetylsalicylic acid in an amount of from 25% to 40% by weight, preferably from 30% to 40% by weight, paracetamol in an amount of from 25% to 40% by weight, preferably from 30% to 40% by weight, and caffeine from 4% to 15% by weight, preferably from 7% to 8 % by weight.

The combined oral formulation is prepared by a simple, not demanding, technological process, not requiring any special manufacturing facilities for granulation, without necessity of enhanced safety modifications of the workspace and equipment.

By the use of stearic acid, the substance responsible for the achieved effect, i.e. prolonged release of acetylsalicylic acid and the pharmaceutical excipients starch and lactose used in various premixes, by their mutual weight ratios and by their technological processing, compression into tablets produces the desired release profile of acetylsalicylic acid and a long-term stable product. The oral tablets, prepared by the method of the invention, comply with the stability requirement of a formulation comprising a combination of the active ingredients acetylsalicylic acid, at least one further active ingredient from the group of non-narcotic analgesics and/or natural psychotropic agents, with the desired release profile of acetylsalicylic acid, without the necessity of any further treatment, e.g., by coating the tablets with a film coat.

The manufacture of combined oral tablets substantially consists in preparation of premixes of the individual active ingredients.

The manufacture of an acetylsalicylic premix in principle comprises simple mixing of acetylcsalicylic acid and the pharmaceutical excipients, stearic acid and starch, in a specific ratio, moisturizing the mixture during mixing, drying, sieving, and final blending until a visually homogeneous mixture is formed.

The manufacture of a paracetamol premix in principle comprises simple mixing of paracetamol and the pharmaceutical excipient (preferably corn starch), moisturizing the mixture with a starch paste until formation of the required structure of the granulation material, drying the same and modification of the particle size of the granulate.

The manufacture of a caffeine triturate in principle comprises simple mixing of caffeine and the pharmaceutical excipient, preferably lactose, followed by blending the resulting mixture with starch.

The final tabletting blend is prepared by mixing of the individual active ingredients premixes with addition of a glidant facilitating the flowability of the tabletting blend and formation of pressings having the desired weight, strength and friability, which are chemically and physically stable for a sufficiently long period of time and can be filled into commonly used pharmaceutical packages without any problems.

The combined oral formulation with controlled release of acetylsalicylic acid according to a preferred embodiment of the present invention comprises, in addition to the three active ingredients - acetylsalicylic acid, paracetamol and caffeine –, pharmaceutically acceptable excipients, namely:

a) stearic acid;
b) corn starch;
c) lactose.

It has been surprisingly found and confirmed that the profile of release of the acetylsalicylic acid active ingredient from a therapeutic composition, prepared according to the present invention, can be set up to the requirements by the ratio of stearic acid and starch in the acetylsalicylic premix. Further, it has been surprisingly found that acetylsalicylic acid, which undergoes hydrolysis, can be granulated with purified water without decomposition thereof and, moreover, it has been found that acetylsalicylic acid can be stabilized by mixing with stearic acid.

The manufacture of a solid therapeutic formulation according to the present invention substantially consists in mixing, in a high-speed pharmaceutical homogenizer for wet homogenization, paracetamol together with a starch, preferably with a starch having a moisture content of from 3% to 25%, in an amount of from 5% to 20% by weight. The said mixture is gradually moisturized with a starch paste, wherein starch amounts to 10% to 50% by weight of said paste. The mixture is shortly mixed until a granulate is formed. The

prepared granulate is dried by the chamber, fluidized, vacuum or microwave radiation method, preferably in fluidized state to obtain a final moisture content between 0.1% and 2.0% by weight. Temperatures of the product during drying should be 35°C to 45°C, preferably 39°C to 41°C. The dried granulate is treated to obtain particle sizes compliant with the tabletting process and homogenized. After complete homogenization the mixture can be used for a tabletting process. A caffeine triturate is admixed to the previously prepared paracetamol granulate, an acetylsalicylic acid granulate and silicon oxide are admixed to the resulting mixture and the final blend is tabletted in rotatory tabletting machines to pressings which have a break resistance of from 20 N to 90 N, preferably from 35 N to 75 N and a disintegration of from 30 seconds to 2 minutes and 30 seconds.

The tablets can be of a flat rounded, lens rounded, oval or other shape, with possible presence of a break line or logo on one or both surfaces of the tablet.

The thus manufactured tablets can be filled into commonly applicable packages destined for pharmaceutical products, preferably into blister packages constituted by PVC/PVdC combination heat-shapable foil and an aluminum foil coated with an adhesive material.

Brief Description of Drawings

Results of a dissolution test (acetate buffer pH 4.5; 500 ml; 50 rpm):

Figure 1: Dissolution profile of acetylsalicylic acid processed in a granulate without stearic acid (acetate buffer pH 4.5; 500 ml; 50 rpm).

Figure 2: Dissolution profile of acetylsalicylic acid processed in a granulate with stearic acid (acetate buffer pH 4.5; 500 ml; 50 rpm).

Examples

The invention is illustrated in the following example, without being limited thereby in any manner.

Example 1

a) Tablet composition

composition of acetylsalicylic granulate	*% by weight*
acetylsalicylic acid	37.30

corn starch	4.66
stearic acid	2.94
composition of paracetamol granulate	*% by weight*
paracetamol	37.30
corn starch	4.71
composition of caffeine triturate	*% by weight*
caffeine	7.46
lactose	3.26
corn starch	2.24
excipients	*% by weight*
silicon oxide	0.096
purified water	q. s.

b) Preparation method

Acetylsalicylic acid is mixed with corn starch and stearic acid having a particle size up to 100 μm in a pharmaceutical granulator of a suitable type. The resulting mixture is then gradually moisturized with purified water until a granulate forms. The latter is transferred into the receptacle of a fluid dryer and dried under slight fluidization at the temperature of the inlet air of 41°C, until the temperature of the granulate reaches 40°C, which indicates completion of the drying process. The dried granulate is then subjected to sizing through an oscillating screen with mesh of 1.0 mm, followed by homogenizing in a homogenizer.

Paracetamol is mixed with corn starch in a pharmaceutical granulator of a suitable type. The resulting mixture is then gradually moisturized with corn paste until a granulate forms. The latter is transferred into the receptacle of a fluid dryer and dried under slight fluidization at the temperature of the inlet air of 55 – 60°C, until the temperature of the granulate reaches 42°C. The dried granulate is then subjected to sizing through an oscillating screen with mesh of 1.25 mm and, subsequently, it is transferred into the receptacle of a fluid dryer and dried until the moisture content of the granulate reaches 1.5 %, measured at 90°C/30 minutes.

Caffeine is mixed with lactose in a low-speed homogenizer of a suitable type. The triturate is subjected to sizing through an oscillating screen with mesh of 0.8 mm. Corn starch is added to the sieved triturate.

The required amounts of the premixes of the individual active ingredients are homogenized in a low-speed homogenizer by dry homogenization with addition of a glidant, which is silicon oxide.

In this manner the composition is prepared for tabletting in rotatory tabletting machines to pressings containing the desired three active ingredients, having satisfactory content uniformity of caffeine, break resistance and disintegration.

c) Results of a stability test:

The following table shows the values of free salicylic acid, measured during storage in various stress conditions. Free salicylic acid is formed as a degradation product of acetylsalicylic acid by the action of hydrolysis.

Storage time	Salicylic acid
Start	0.06%
Storage conditions 25°C ± 2°C; RH 60% ± 5%	
3 months	0.09%
18 months	0.24%
Storage conditions 30°C ± 2°C; RH 65% ± 5%	
3 months	0.12%
12 months	0.42%
Storage conditions 40°C ± 2°C; RH 75% ± 5%	
3 months	0.75%
6 months	1.98%

Claims

1. A combined oral formulation with controlled release of acetylsalicylic acid, characterized in that the formulation comprises at least one further active ingredient selected from the group consisting of non-narcotic analgesics and natural psychotropic agents, and the excipients starch and stearic acid.

2. The formulation according to claim 1, characterized in that the non-narcotic analgesic is paracetamol and/or ibuprofen.

3. The formulation according to claims 1 or 2, characterized in that natural psychotropic agent is caffeine.

4. The formulation according to any one of claims 1-3, characterized in that it comprises acetylsalicylic acid and a mixture of stearic acid and starch in a ratio of from 2:1 to 10:1.

5. The formulation according to any one of claims 1-4, characterized in that it comprises stearic acid in an amount of from 1% to 5% by weight, preferably from 1.5% to 3% by weight, and starch in an amount of from 2% to 10% by weight, preferably from 4% to 5% by weight.

6. The formulation according to any one of claims 1-5, characterized in that the particle size of stearic acid is in the range of from 1 to 100 μm.

7. The formulation according to claim 6, characterized in that up to 90% of stearic acid has a particle size of from 1 to 20 μm.

8. The formulation according to any one of claims 1-7, characterized in that the starch is corn starch, potato starch and/or rice starch.

9. The formulation according to claim 8, characterized in that the starch is corn starch.

10. The formulation according to claim 9, characterized in that the starch is corn starch with a moisture content of from 3% to 20%, preferably from 11% to 18%.

11. The formulation according to any one of claims 1 to 10, characterized in that the final blend comprises acetylsalicylic acid and paracetamol.

12. The formulation according to claim 11, characterized in that the final blend comprises acetylsalicylic acid and paracetamol in separate granules.

13. The formulation according to claim 12, characterized in that the acetylsalicylic acid granulate comprises starch and stearic acid as excipients in a mutual ratio of about 1.58 : 1.

14. The formulation according to claim 12, characterized in that the paracetamol granulate comprises starch as an excipient.

15. The formulation according to any one of claims 1-14, characterized in that the final blend comprises a third active ingredient, which is caffeine, in the form of a triturate.

16. The formulation according to claim 15, characterized in that the caffeine triturate comprises lactose and starch as excipients in a mutual ratio of about 1.46 : 1.

17. The formulation according to claim 15, characterized in that it comprises acetylsalicylic acid at from 25% to 40% by weight, preferably from 30% to 40% by weight, paracetamol at from 25% to 40% by weight, preferably from 30% to 40% by weight, and caffeine at from 4% to 15% by weight, preferably from 7% to 8% by weight.

18. A method for the preparation of a combined oral formulation with controlled release of acetylsalicylic acid according to any one of claims 1-17, characterized in that a caffeine triturate is admixed to a previously prepared paracetamol granulate, an acetylsalicylic acid granulate and silicon oxide are admixed to the resulting mixture and the final blend is tabletted to pressings which have a break resistance of from 20 N to 90 N, preferably from 35 N to 75 N, and a disintegration of from 30 seconds to 2 minutes and 30 seconds.

19. The method according to claim 18, characterized in that the acetylsalicylic acid granulate is prepared by mixing acetylsalicylic acid in an admixture with stearic acid and starch, the mixture being moisturized with purified water during mixing, thus forming a granulate.

20. The method according to claim 18, characterized in that the paracetamol granulate is prepared by mixing paracetamol with starch, the mixture being moisturized with starch paste during mixing, thus forming a granulate.

21. The method according to claims 19 or 20, characterized in that the acetysalicylic acid and paracetamol granulates are individually dried by the chamber, vacuum fluidized, or microwave radiation method to obtain a residual moisture content between 0.1% and 2.0% by weight, preferably from 0.5% to 1,5% by weight.

22. The method according to claim 19, characterized in that the acetylsalicylic granulate is dried at a temperature of from 35°C to 45°C, preferably from 39°C to 41°C.

23. The method according to claim 18, characterized in that the caffeine triturate is prepared by mixing caffeine in a mixture with lactose and starch.

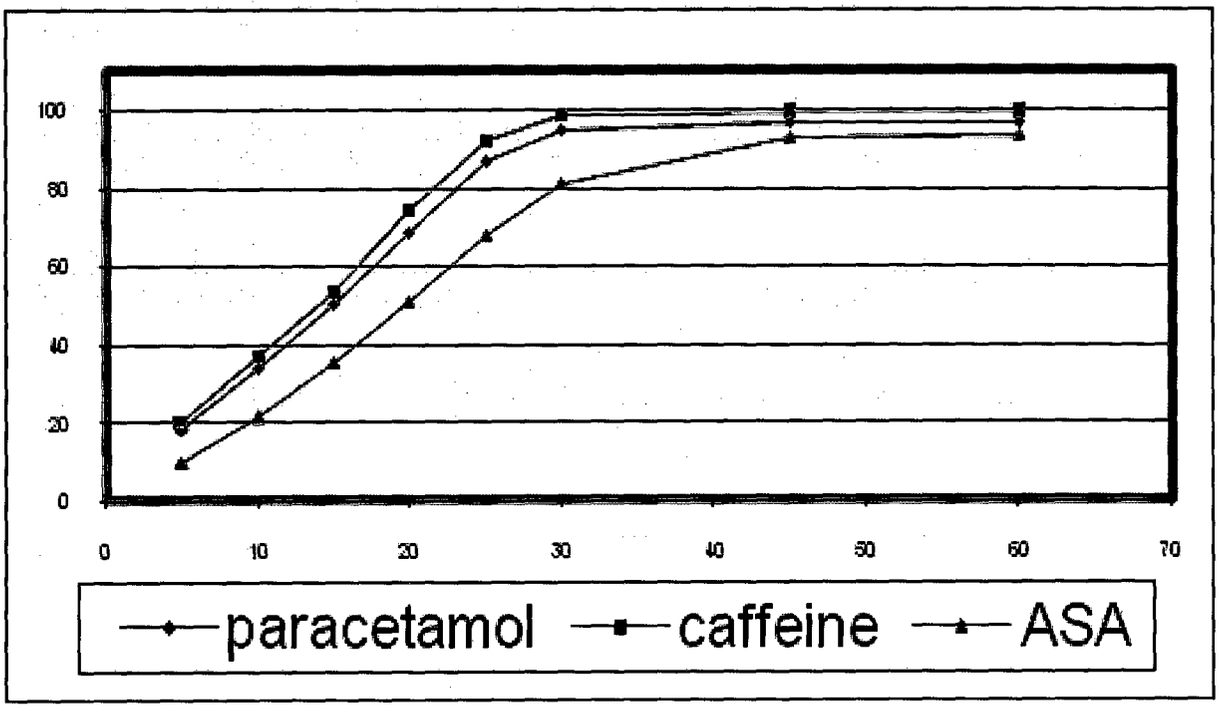

Fig. 1

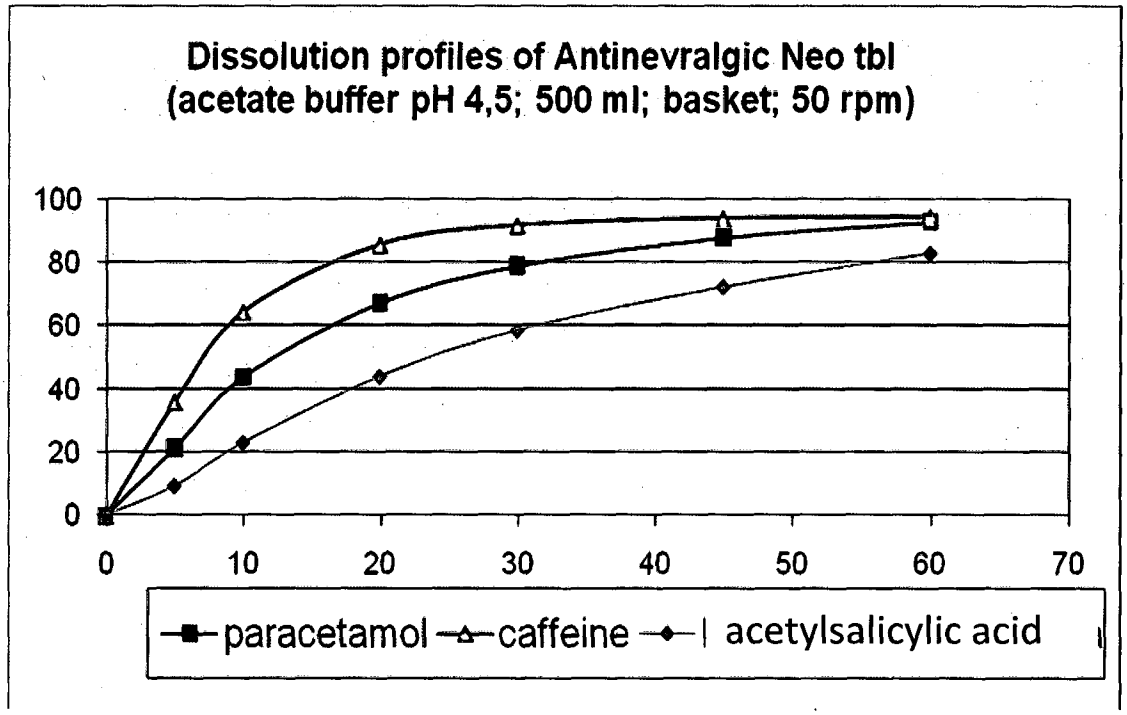
Dissolution profiles of Antinevralgic Neo tbl
(acetate buffer pH 4,5; 500 ml; basket; 50 rpm)
100
80
60
40
20
0
0
10
20
30
40
50
60
70
paracetamol
caffeine
acetylsalicylic acid

Fig. 2