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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 9/20, 31/155	A1	WO 92/03126
		(43) International Publication Date: 5 March 1992 (05.03.92)

(21) International Application Number: PCT/HU91/00039

(22) International Filing Date: 23 August 1991 (23.08.91)

(30) Priority data:
5314/90 24 August 1990 (24.08.90) HU

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(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, PL, SE (European patent), US.

Published
With international search report.

(54) Title: PROCESS FOR THE PREPARATION OF A TABLET OR DRAGEE COMPOSITION CONTAINING A HEAT-, LIGHT- AND MOISTURE-SENSITIVE ACTIVE INGREDIENT HAVING MONOCLINIC CRYSTAL STRUCTURE

(57) Abstract

The invention relates to a process for the preparation of a tablet or dragée composition containing a moisture-, heat- and light-sensitive compounds having monoclinic crystalline structure as active ingredients, which comprises homogenizing the active ingredient with 0.2 to 1.5 parts by weight of an anhydrous alkaline earth metal salt and 0.5 and 2.5 parts by weight of microcrystalline cellulose calculated for the active ingredient and optionally with one or more pharmaceutically acceptable carrier(s) and/or additive(s) and compressing the homogeneous mixture obtained to tablets in a manner known per se and, if desired, coating the tablet thus obtained in a manner known per se.

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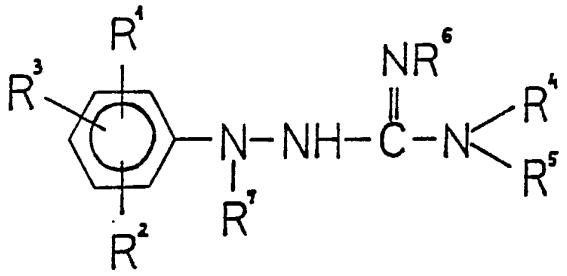
Process for the preparation of a tablet or dragée composition containing a heat-, light- and moisture--sensitive active ingredient having monoclinic crystal structure

The invention relates to a process for the preparation of a tablet or dragée composition containing a heat-, light- and moisture-sensitive active ingredient having monoclinic crystal structure.

The process according to the invention is particularly useful for preparing a pharmaceutical composition having antiarrhythmic activity and containing as active ingredient an aminoguanidine derivative of the general formula (I),



I.

wherein

R^1, R^2 and R^3 stand independently from each other, for hydrogen, halogen or C_{1-4} alkyl, nitro, C_{1-4} alkoxy or trifluormethyl group;

R^4 and R^5 represent independently from each other, a C_{1-4} alkyl group;

R^6 and R^7 represent, independently from each other, hydrogen or C_{1-4} alkyl or C_{2-4} alkenyl group

or their acid addition salts crystallizing in monoclinic

system.

It is very difficult to prepare an oral dosage form such as tablet or dragée from substance having monoclinic crystal structure since the adhesion between the crystal plates is weak and the aggregation of granules is difficult to compress.

According to a method well-proved in the practice for tabletting monoclinic crystalline substances and having weak adhesive properties (e.g. phenylbutazone, phenacetin, barbiturates), the powdered mixture containing the active ingredient is pressed after wet granulation [H.A. Lieberman, L. Lachman: Pharmaceutical Dosage Forms, Tablets, Volume 2, Marcel Dkker, Inc., NY (1981)]. In this case, the binding force needed to the tablet formation is provided by the binding agent introduced during the kneading whereas the optimum compressibility is ensured by the optimum porosity and flowability developed in the preparing procedure carried out in a suitable way.

The wet granulation cannot be carried out and the table formation can be realized only by direct compression or briquetting when the active ingredient crystallizes in monoclinic system and is also sensitive to moisture (e.g. salycilic acid derivatives). In this case the necessary adhesion is ensured partly by the solid binding agent introduced as a powder mixture and partly by the binding forces developed at the so-called active sites of the granule surfaces [A.S. Rankel et al.: J. Pharm. Soc. 57, 574 (1968)].

In cases of moisture- and light-sensitive substances, the tablets should be provided with a protective coat to prevent any damage during the storage. A tablet prepared by direct compression should possess an appropriate hardness in order to be useful for a further processing, e.g. dragée formation.

The hardness can be enhanced by increasing the force of compression, however, the density of tablet is increased and the porosity thereof is decrased by enhancing the force of compression. The disintegration of the tablet is decisively influenced by the porosity since the higher the density of the tablet is, the slower is the penetration of the aqueous fluid thus, the dissolution of the active ingredient from a tablet of high density is very slow, the desired blood level of the acitve ingredient can be achieved only after a long period and the bioavailability of the active ingredient is also low.

During compression a heat effect is developed by the friction of the granules, whereby the heat-sensitive active ingredients are usually decomposed thus, a direct compression or briquetting cannot be employed in these cases.

As a consequence, it is a very difficult task to formulate monoclinic crystalline compounds simultaneously being sensitive to moisture, heat and light effects to tablet composition. No literature reference has been found for the solving of this problem.

The aim of the present invention is to work out a composition, which is useful for the preparation of a tablet or dragée core from monoclinic moisture-, heat- and light-sensitive compounds by compression. A further aim of the present invention is to prepare a tablet or dragée composition making possible the rapid absorption of the active ingredient as well as the development of high blood levels after taking the composition and resulting in a high bioavailability of the active ingredient.

Surprisingly, it has been found that the above aims can be achieved by adding 0.2 to 1.5 parts by weight of

an anhydrous alkaline earth metal salt and 0.5 to 2.5 parts by weight of microcrystalline cellulose calculated form the active ingredient, to the moisture-, heat- and light-sensitive active ingredient having monoclinic crystalline structure.

Thus, the present invention relates to the preparation of a tablet or dragée composition from moisture-, heat- and light-sensitive active ingredient having monoclinic crystalline structure, which comprises homogenizing the active ingredient with 0.2 to 1.5 parts by weight of an anhydrous alkaline earth metal salt and 0.5 to 2.5 parts by weight of microcrystalline cellulose calculated for the active ingredient as well as, if desired, with one or more pharmaceutically acceptable carrier(s) and/or additive(s) and compressing the homogeneous mixture thus obtained to tablets in a manner known per se and, if desired, coating the tablet obtained in a manner known per se.

The invention is based on the recognition that a tablet with suitable breaking strength can be prepared by using relatively low pressure of 150 to 200 MPa, when a tablet is compressed in such a way that a defined amount of an anhydrous alkaline earth metal salt and microcrystalline cellulose are added to the monoclinic moisture-, heat- and light-sensitive active ingredient. In this case, no increase in the free energy occurs at the binding sites, which could induce a chemical change, i.e. the decomposition of the active ingredient since the displacement at the binding sites of the mobile anions being present in the crystal structure of the active ingredient is inhibited by the alkaline earth metal salt and simultaneously, a tablet can be obtained which is suitably solid for coating, conveniently disintegrates in the stomach and advantageously releases the active ingredient.

In the process of the invention, e.g. calcium or magnesium hydrogen phosphate, calcium or magnesium dihydrogen phosphate or sulfate or carbonate may be used as anhydrous alkaline earth metal salts.

Suitable pharmaceutically acceptable carriers in the preparation of the invention are e.g. talc, maize starch, magnezium stearate, colloidal silica (Aerosil 200), lactose, glucose, mannitol or the like.

Suitable additives are e.g. one or more binding agent(s), antioxidant(s) disintegrating or flowability--promoting additive(s).

Useful binding agents are e.g. polyvinylpyrrolidone, vinylpirrolidone/vinyl acetate copolymer (Luwiskol VA 64) or polyethylene glycols.

Useful antioxidants are e.g. ascorbic acid or sodium disulfide.

The active ingredient content of the composition according to the invention may be varied between broad limits depending from the nature of the active ingredient, type of the disease to be treated, dose of the active ingredient to be used and the like. The active ingredient content of the composition is preferably 0.5 to 50% by weight.

The composition according to the invention contains the alkaline earth metal salt and microcrystalline cellulose in an amount of 2 to 90% by weight, preferably in an amount of 30 to 75% by weight.

The tablets are prepared by homogenizing the ingredients and then by compressing the homogeneous mixture obtained by using a pressure of 150 to 200 MPa in a known manner.

If desired, the tablet may be provided with a coat.

The coat has to satisfy two demands: on the one hand, the active ingredient should be protected against the harmful effect of light and air moisture and on the

other hand, a suitable dissolution of the active ingredient has simultaneously to be ensured.

Since the active ingredient is sensitive to moisture, no aqueous system can be used and an organic solvent can only by considered for coating.

The coat conveniently contains a hydrophilic component (such as polyethylene glycol, water-soluble cellulose ethers or vinylpirrolidone/vinyl acetate copolymer) and a hydrophobic component (ethylcellulose or acrylate/metacrylate ester copolymer). The weight ratio of hydrophilic components to the hydrophobic components is preferably 1:1 to 1:1.5.

Pharmaceutically acceptable organic solvents being capable to dissolve the components of the coat, such as alcohols and ketones, e.g. ethanol, isopropanol, acetone or their mixtures may be used as solvents for coating material.

The mixture containing ethanol/acetone or isopropanol/acetone in a volume ratio of 1:0.2 to 1:1.5 is preferred as solvent.

The coating process is carried out by using a suspension prepared with an organic solvent containing the hydrophilic and hydrophobic substances and optionally other additives (e.g. light-protevtive dyes such as an iron oxide pigment) in a known manner.

The process according to the invention is particularly useful for preparing an antiarrhythmic active pharmaceutical composition composition containing as active ingredient an aminoguanidine derivative of the general formula (I), wherein

R^1, R^2 and R^3 stand independently from each other, for hydrogen, halogen or C_{1-4} alkyl, nitro C_{1-4} alkoxy or trifluormethyl group;

R^4 and R^5 represent independently from each other, a C_{1-4} alkyl group;

R^6 and R^7 represent, independently from each other, hydrogen or C_{1-4} alkyl or C_{2-4} alkenyl group or their acid addition salts crystallizing in monoclinic system.

The aminoguanidine derivatives of general formula (I) and their acid addition salts are moisture-, light- and heat-sensitive and are transformed to vivid red-coloured phenylazoformamidine derivatives by an auto-oxidation reaction.

When the hydrochloride of 1-(2,6-dimethylphenyl)--4,4'-dimethylaminoguanidine being within the scope of the general formula (I) is subjected to a wet granulation according to known processes and then compressed to tablets (shown in Example 1), then the active ingredient of the compsition significantly decomposes within a short time interval (e.g. 10 days). The same decomposition of the active ingredient has not been observed on compositions prepared according to the invention: the composition remained stable during a longer time of storage and even in the case of a higher moisture content.

Based on clinical investigations, on using 1-(2,6--dimethylphenyl)-4,4'-dimethylaminoguanidine hydrochloride being within the scope of the general formula (I) as active ingredient of the composition according to the invention, the half life measured in the blood increased from 2.4 hours to 3.2 hours in comparison to an injectable composition containing the same active ingredient, whereas the relative bioavailability of the active ingredient proved to be about 80%.

The process according to the invention is illustrated in detail by the following non limiting Examples.

1-(2,6-Dimethylphenyl)-4,4'-dimethylaminoguanidine hydrochloride was used as active ingredient in all these

Examples. The amounts given in the Examples mean parts by weight (pbw) in each case when it is not noted otherwise.

Comparative example 1

Ingredients	Amounts
Active ingredient	500
Lactose	1005
Maize starch	900
Microcrystalline cellulose	420
Polyvinylpyrrolidone	85
Ascorbic acid	30
Magnesium stearite	20
Talc	40

The active ingredient was admixed with maize starch, microcrystalline cellulose and lactose. Polyvinylpyrrolidone and ascorbic acid were dissolved in 800 ml of ethanol and the homogeneous mixture was granulated with the latter solution. Aftyer drying, the granulate was homogenized with the substances of the outer phase and then compressed to flat edge tablets weighing 300 mg each by using a compression pressure of 100 to 150 MPa. The breaking strength of the tablets was 50 to 75 N.

The tablets obtained were subjected to storage experiments carried out in the presence of moisture and heat as well as light load. According to our observations the colour of the tablet became deeper and a decomposition product of 1 to 2% by weight could be detected at a temperature of 60°C or at room temperature in the presence of a relative moisture content of 80% during 10 days. This decomposition process could not be prevented by ascorbic acid.

Example 2

Ingredients	Amounts
Active ingredient	500

Lactose	810
Maize starch	900
Colloidal silicon dioxide	15
Polyvinylpyrrolidone	85
Microcrystalline cellulose	600
Ascorbic acid	30
Talc	40
Magnesium stearate	20

The sieved components with the prescribed particle size were carefully homogenized and the aggregation of granules obtained was compressed to biconvex tablets of 10 mm in diameter weighing 300 mg each by using a compression pressure of 150 MPa on a rotating tablet machine.

The tablets possess a breaking trength of 40 to 50 N.

Example 3

Ingredients	**Amounts**
Active ingredient	1000
Maize starch	660
Anhydrous calcium hydrogen phosphate	900
Microcrystalline cellulose	1540
Vinylpyrrolidone/vinyl acetate copolymer	160
Talc	120
Ascorbic acid	60
Magnesium stearate	40
Colloidal silica	20

The sieved components with the prescribed particle size were carefully homogenized and the aggregation of granules obtaind was compressed to biconvex tablets of 9 mm in diameter weighing 300 mg each by using a compression pressure of 150 MPa on a rotating tablet machine.

The tablets possess a breaking strength of 50 to 80

N.

The dragée scores obtained as described above were coated with a suspension containing the ingredients listed below in a pan suitable for film coat formation.

Ingredients	g
Ethylcellulose	56
Vinylpyrrolidone/vinyl acetate copolymer	56
Talc	68
Magnesium stearate	10
Titanium dioxide	4
Yellow iron oxide pigment	6
Ethanol	1080
Acetone	1000

The tablet prepared as described above was stored in a relative moisture content of 75% and 95%, respectively for 12 months. The results are shown in Table I.

Table I

Months	Relative moisture content 75%		95%	
	mg/tablet	decomp.%	mg/tablet	decomp.%
0	49.85	0	0	0
1	49.82	0.09	50.17	0.2
2	49.22	0.10	49.82	0.1
4	49.73	0.90	49.37	1.7
12	49.98	0.05	-	-

In order to determine the heat-stability, the tablets were stored at 24, 40, 50 or 60°C, respectively for 12 months. The results are shown in Table II.

Table II

Time of storage months	Temperature 24°C		40°C		50°C		60°C	
	mg/tab.	dec.%	mg/tab.	dec.%	mg/tab.	dec.%	mg/tab.	dec.%
0	-	-	-	-	-	-	-	-
1	-	-	-	-	49.06	0.25	49.04	0.09
2	-	-	48.88	0.13	48.35	0.13	48.23	0.13
4	-	-	48.06	0.40	48.00	0.60	47.32	0.13
8	52.32	0.35	49.10	-	-	-	-	-
12	51.06	0.45	-	-	-	-	-	-

The absorption of the active ingredient from the tablet prepared as described above was investigetad in dogs. The composition showed an absorption coefficient (k_a) of 0.9 to 1.6 h^{-1} and an elimination coefficient (k_e) of 0.20 to 0.25 h^{-1}, i.e. the values indicate a rapid absorption.

The preceding results were supported by pharmacokinetic examinations carried out in the human I phase clinical trials. A value of 1.4 h^{-1} was obtained for the absorption coefficient (k_a) in the human trials. The relative bioavailabilty calculated from the AUC values proved to be 80%. This value can be considered to be very high as a part of the antiarrhytmic reference drugs (e.g. aminodarone) were not absorbed and a bioavailability of 40 to 70% has only been achieved in case of other drugs (e.g. quinidine, lidocaine) [P. G. Welling et al.: Pharmacokinetics of Cardiovascular, Central Nervous System and Antimicrobial Drugs, London, (1985)].

Example 4

Ingredients	**Amounts**
Active ingredient	1000
Maize starch	600
Anhydrous calcium hydrogen phosphate	900

Microcrystalline cellulose	1800
Vinylpyrrolidone/vinyl acetate copolymer	160
Talc	120
Ascorbic acid	60
Magnesium stearate	40
Colloidal silica	20

After crushing and sieving to the desired particle size, the components were carefully homogenzied, then the aggregation of granules obtained was compressed to biconvex tablets of 11 mm in diameter weighing 430 g each by using a compression pressure of 200 MPa on a rotating tablet machine.

The tablets possess a breaking strength of 80 to 100 N.

The dragée scores were uniformly coated in an automated dragée-forming apparatus with a suspension containing the following ingredients.

Ingredients	**g**
Acrylic acid/metacrylic acid copolymer	60
Polyethylene glycol 600	40
Talc	80
Magnesium stearate	10
Titanium dioxide	4
Yellow iron oxide pigment	6
Isopropanol	1000
Acetone	900

Example 5

Ingredients	**Amount**
Active ingredient	2000
Maize starch	110
Anhydrous calcium hydrogen phosphate	450
Microcrystalline cellulose	1200

Polyvinylpyrrolidone	200
Talc	120
Sodium disulfite	50
Magnesium stearate	40
Colloidal silica	30

The sieved components with the prescribed particle size are carefully homogenzied, then the aggregation of granules obtained is compressed to biconvex tablets of 11 mm in diameter weighing 420 mg each by using a compression pressure of 150 MPa on a rotating tablet machine.

The tablets possess a breaking strength of 90 to 100 N.

The tablet scores are uniformly coated in an automated dragée-forming apparatus with a suspension containing the following ingredients:

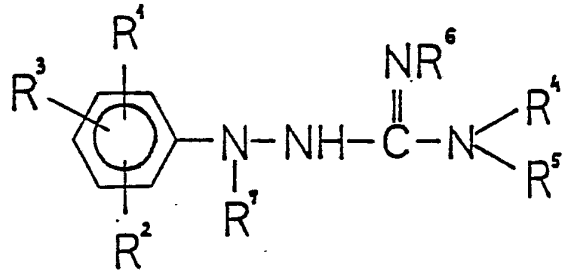
Ingredients	**g**
Ethylcellulose	58
Hydroxypropylcellulose	50
Talc	70
Magnesium stearate	11
Titanium dioxide	3
Red iron oxide pigment	8
Ethanol	1800
Acetone	400

What is claimed is:

1. A process for the preparation of a tablet or dragée composition containing a moisture-, heat- and light-sensitive compounds having monoclinic crystalline structure as active ingredients, which **comprises** homogenizing the active ingredient with 0.2 to 1.5 parts by weight of an anhydrous alkaline earth metal salt and 0.5 to 2.5 parts by weight of microcrystalline cellulose calculated for the active ingredient and optionally with one or more pharmaceutically acceptable carrier(s) and/or additive(s) and compressing the homogeneous mixture obtained to tablets in a manner known per se and, if desired, coating the tablet thus obtained in a manner known per se.

2. A process as claimed in claim 1, which **comprises** using calcium or magnesium hydrogen phosphate, dihydrogen phosphate, hydrogen carbonate, carbonate or sulfate as an alkaline earth metal salt.

3. A process as claimed in claim 1, which **comprises** using as active ingredient an aminoguanidine derivative of the general formula (I), having monoclinic crystalline structure,



I.

wherein

R^1, R^2 and R^3 stand independently from each other, for

hydrogen, halogen or C_{1-4} alkyl, nitro, C_{1-4} alkoxy or trifluormethyl group;

R^4 and R^5 represent independently from each other, a C_{1-4} alkyl group;

R^6 and R^7 represent, independently from each other, hydrogen or C_{1-4} alkyl or C_{2-4} alkenyl group

or an acid addition salt thereof.

4. A process as claimed in claim 3, which **comprises** using 1-(2,6-dimethylphenyl)-4,4'-dimethylaminoguanidine hydrochlorid as active ingredient.

5. A process as claimed in claim 1, which **comprises** homogenizing as active ingredient 1-(2,6-dimethyl-phenyl)-4,4'-dimethylaminoguanidine hydrochloride with 0.2 to 1.5 parts by weight of anhydrous calcium hydrogen phosphate and 0.5 to 2.5 parts by weight of micro-crystalline cellulose calculated for the active ingredient and optionally with one or more pharma-ceutically acceptable carrier(s) and/or additive(s), then compressing the homogeneous mixture obtained to tablets in a manner known per se and, if desired, coating the tablet obtained in a manner known per se.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 91/00039

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[5]: A 61 K 9/20, A 61 K 31/155

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[5]	A 61 K 9/00, A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

AT

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4 198 402 (E. EZER et al.) 15 April 1980 (15.04.80), see abstract; claim 1; column 5, lines 6-25.	(1)
A	GB, A, 1 480 188 (BAYER AKTIENGESELLSCHAFT) 20 July 1977 (20.07.77), see page 2, lines 50-94; page 2, line 120 - page 3, line 46.	(1,2)
A	EP, A1, 0 124 027 (PENNWALT CORPORATION) 07 November 1984 (07.11.84), see claims 1-8; page 4, line 16 - page 5, line 19; examples 1-8.	(1,2)
A	EP, A2, 0 112 061 (BEECHAM GROUP PLC) 27 June 1984 (27.06.84), see abstract; formulation 1.	(1,3-5)
A	US, A, 3 868 463 (D.C. REMY) 25 February 1975 (25.02.75), see example 5; abstract.	(1-5)
A	US, A, 3 907 999 (M.E. CHRISTY) 23 September 1975 (23.09.75), see example 41; abstract.	(1-5)
A	EP, A1, 0 210 661 (STAUFFER CHEMICAL COMPANY) 04 February 1987 (04.02.87), see abstract; column 11, lines 32-43; claims 26-29.	(1,2)
A	EP, A2, 0 193 984 (FMC CORPORATION) 10 September 1986 (10.09.86), see abstract; page 1, line 23 - page 2, line 32.	(1,2)

* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
01 October 1991 (01.10.91)	09 October 1991 (09.10.91)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 91/00039

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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