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(54) Titre : PROCEDE DE PREPARATION D'UNE COMPOSITION EN COMPRIMES OU EN DRAGEES CONTENANT UN PRINCIPE ACTIF SENSIBLE A LA CHALEUR, A LA LUMIERE ET A L'HUMIDITE AYANT UNE STRUCTURE CRISTALLINE MONOCLONIQUE

(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) Abrégé/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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(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.		

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

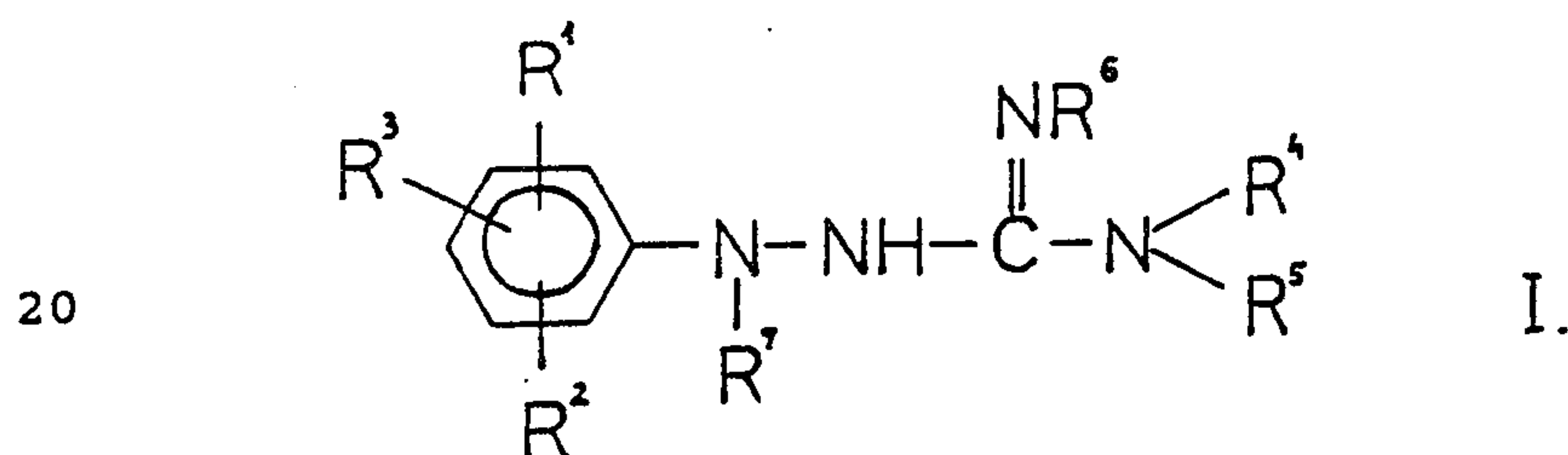
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The invention relates to a process for the preparation of a tablet or dragée composition containing a heat-, light- and moisture-sensitive active ingredient having monoclinic crystal structure.

10

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),

15



25

wherein

R¹, R² and R³ stand independently from each other, for hydrogen, halogen or C₁₋₄ alkyl, nitro,

30

C₁₋₄ alkoxy or trifluormethyl group;

R⁴ and R⁵ represent independently from each other, a C₁₋₄ alkyl group;

R⁶ and R⁷ represent, independently from each other, hydrogen or C₁₋₄ alkyl or C₂₋₄ alkenyl group

35 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 tableting 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 Dekker, 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. salicylic 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 decreased by enhancing the force of compression. The disintegration
5 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
10 the active 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
15 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
20 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
25 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
30 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
35 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 from the active ingredient, to the moisture-, heat- and light-sensitive active ingredient having monoclinic
5 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
10 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
15 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
20 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
25 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
30 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
35 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.

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

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

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

15 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
20 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
25 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
30 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
35 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
5 only be considered for coating.

The coat conveniently contains a hydrophilic component (such as polyethylene glycol, water-soluble cellulose ethers or vinylpyrrolidone/vinyl acetate copolymer) and a hydrophobic component (ethylcellulose
10 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
15 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
20 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-protective dyes
25 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 containing as active ingredient an aminoguanidine derivative of the
30 general formula (I), wherein

R¹, R² and R³ stand independently from each other, for hydrogen, halogen or C₁₋₄ alkyl, nitro

C₁₋₄ alkoxy or trifluormethyl group;

R⁴ and R⁵ represent independently from each other, a

35 C₁₋₄ alkyl group;

R⁶ and R⁷ represent, independently from each other, hydrogen or C₁₋₄ alkyl or C₂₋₄ alkenyl group or their acid addition salts crystallizing in monoclinic system.

5 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.

10 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
15 active ingredient of the composition 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
20 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
25 (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
30 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
35 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

5	Ingredients	Amounts
	Active ingredient	500
	Lactose	1005
	Maize starch	900
	Microcrystalline cellulose	420
10	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
35	Active ingredient	500

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

10 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.

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

Example 3

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

30 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.

35 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.

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

15 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

20	Months	Relative moisture content			
		75%		95%	
		mg/tablet	decomp. %	mg/tablet	decomp. %
25	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	-	-

30 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

5	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
10	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 investigated 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 bioavailability calculated from the AUC values proved to be 80%. This value can be considered to be very high as a part of the antiarrhythmic 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

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

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

After crushing and sieving to the desired particle size, the components were carefully homogenized, then
10 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
15 N.

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

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

	Example 5	
30	Ingredients	Amount
	Active ingredient	2000
	Maize starch	110
	Anhydrous calcium hydrogen phosphate	450
35	Microcrystalline cellulose	1200

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

The sieved components with the prescribed particle size are carefully homogenized, then the aggregation of granules obtained is compressed to biconvex tablets of 11 mm in diameter weighing 420 mg each by using a
10 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
15 dragée-forming apparatus with a suspension containing the following ingredients:

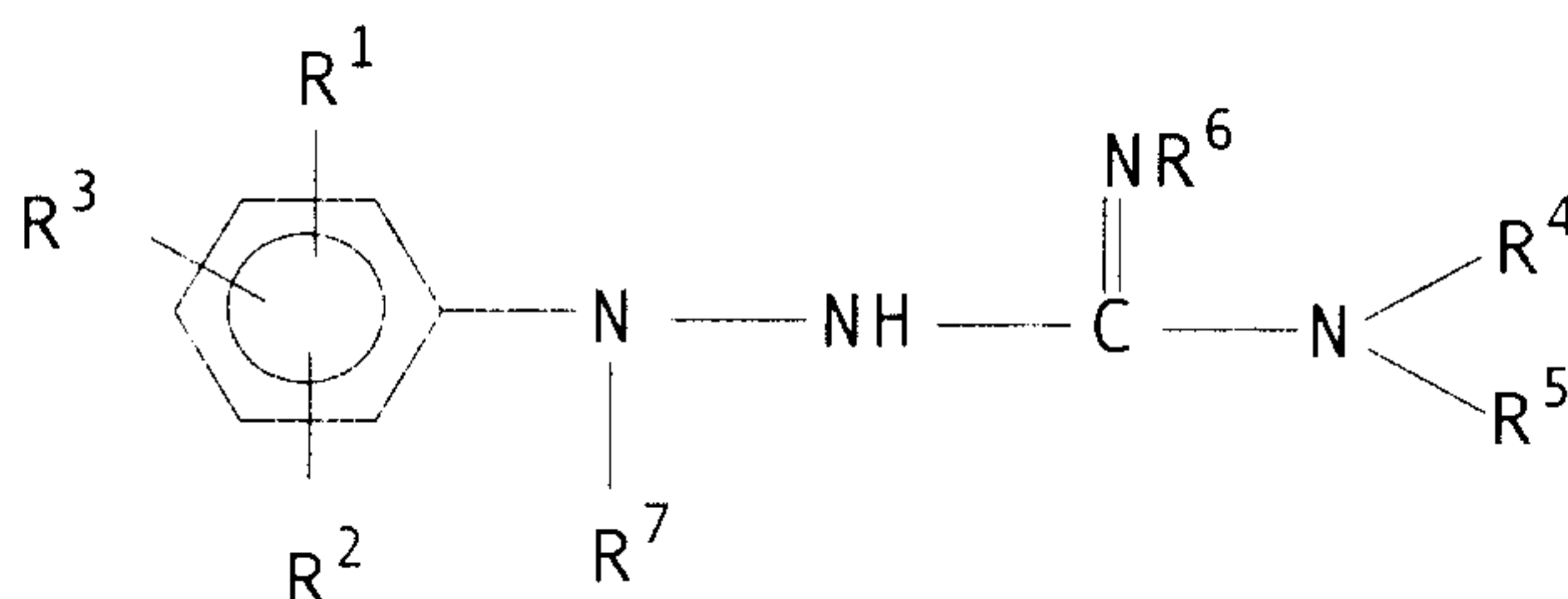
	Ingredients	g
	Ethylcellulose	58
	Hydroxypropylcellulose	50
20	Talc	70
	Magnesium stearate	11
	Titanium dioxide	3
	Red iron oxide pigment	8
	Ethanol	1800
25	Acetone	400

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CLAIMS:

1. A process for the preparation of a tablet or dragée composition, which comprises homogenizing an aminoguanidine derivative of the general formula (I), having monoclinic
5 crystalline structure,



10

(I)

wherein

R¹, R² and R³ stand, independently from each other, for hydrogen, halogen or C₁₋₄ alkyl, nitro, C₁₋₄ alkoxy or trifluoromethyl group;

- 15 R⁴ and R⁵ represent, independently from each other, a C₁₋₄ alkyl group;

R⁶ and R⁷ represent, independently from each other, hydrogen or C₁₋₄ alkyl or C₂₋₄ alkenyl group or an acid addition salt thereof with 0.2 to 1.5 parts by weight of an anhydrous
20 alkaline earth metal salt and 0.5 to 2.5 parts by weight of microcrystalline cellulose calculated for the aminoguanidine derivative and compressing the homogeneous mixture obtained to tablets.

2. A process as claimed in claim 1, wherein the
25 aminoguanidine derivative, anhydrous earth metal salt and microcrystalline cellulose are homogenized with one or more pharmaceutically acceptable carriers or additives, or both.

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3. A process as claimed in claim 1 or 2, further comprising the step of coating the tablets.

4. A process as claimed in any one of claims 1 to 3, which comprises using calcium or magnesium hydrogen phosphate,
5 dihydrogen phosphate, hydrogen carbonate, carbonate or sulfate as the alkaline earth metal salt.

5. A process as claimed in any one of claims 1 to 4, which comprises using 1-(2,6-dimethylphenyl)-4,4'-
dimethylaminoguanidine hydrochloride as the aminoguanidine
10 derivative.

6. A process as claimed in claim 1, which comprises homogenizing as the aminoguanidine derivative, 1-(2,6-
dimethylphenyl)-4,4'-dimethylaminoguanidine hydrochloride with
0.2 to 1.5 parts by weight of anhydrous calcium hydrogen
15 phosphate and 0.5 to 2.5 parts by weight of microcrystalline cellulose calculated for the aminoguanidine derivative.

7. A process as claimed in claim 6, wherein the aminoguanidine derivative, anhydrous calcium hydrogen phosphate and microcrystalline cellulose are homogenized with one or more
20 pharmaceutically acceptable carriers or additives, or both.

8. A process as claimed in claim 6 or 7, further comprising the step of coating the tablets.

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