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(54) **ORAL PHARMACEUTICAL FORMULATIONS CONTAINING GLICLAZIDE**

GLICLAZID ENTHALTENDE ORALE PHARMAZEUTISCHE FORMULIERUNGEN

FORMULATIONS PHARMACEUTIQUES ORALES CONTENANT DU GLICLAZIDE

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(73) Proprietor: **VALPHARMA S.p.A.
47899 Serravalle (SM)**

(72) Inventors:
• **VALDUCCI, Roberto
I-47039 Savignano Sul Rubicone (IT)**
• **ALIGHIERI, Tiziano
I-47900 Rimini (IT)**
• **AVANESSIAN, Serozh
I-47827 Villa Verucchio (IT)**

(74) Representative: **Valenza, Silvia et al
Notarbartolo & Gervasi S.p.A.
Viale Achille Papa, 30
20149 Milano (IT)**

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- DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 3 July 2007 (2007-07-03), LI, SHENGFEI: "Controlled-release preparation containing dimethylbiguanide HCl and gliclazide and its preparation method" XP002528027 retrieved from STN Database accession no. 2007:717220 & CN 1 985 819 A (BEIJINGRUNDEKANGMEDICALTECHNOLOGY CO., LTD., PEOP. REP. CHINA) 27 June 2007 (2007-06-27)

DescriptionField of the invention

5 **[0001]** The present invention relates to pharmaceutical formulations for oral administration, and particularly to those containing gliclazide.

State of the art

10 **[0002]** Pharmaceutical formulations for oral administration containing gliclazide as the active ingredient are well known.

[0003] The patent WO 0018373 describes the production of core tablets by mixing several types of hydroxypropyl methylcellulose (HPMC) and adding maltodextrin and other diluents.

[0004] The production method involves the following steps:

- 15 -
- mixing all the components except for the HPMC
 - wet granulation with water
 - drying and grading of the granules
 - mixing first with the various types of HPMC to form the delayed-release matrix and then with lubricants
 - compression.
- 20

[0005] A hydrophilic core tablet is thus obtained with a mechanism of release by means of gelification.

[0006] This type of formulation has considerable drawbacks, i.e.

- 25 -
- lengthy and costly process times;
 - the need for ample production areas;
 - the risk of segregating the active ingredient from the granules;
 - contamination and toxicity of the production environments and for the operators involved, due to the dust forming in the various production stages and the considerable handling needed during the production process.

30 **[0007]** On the other hand, patents EP 1064935 and US 6319520 describe the formation of granules by means of thermoforming process using methacrylate derivatives, such as Eudragit RS, RL, E.

[0008] After granulation, which takes place at a temperature coming between 60 and 150°C, the resulting granules are compressed to produce core tablets.

35 **[0009]** The mechanism of release from these tablets is diffusive and it is pH-independent, in particular, in the case of Eudragit RS + Eudragit RL being used.

[0010] This type of formulation has the drawback of demanding a high-temperature extrusion process with a consequent risk of damaging the active ingredient and making the working conditions particularly hazardous.

40 **[0011]** Zhang et al. (STN Database Accession no. 2006:1098308; ZHONGGUO YAOYE, 15(10), 27-29) describes a granule composition comprising gliclazide, microcrystalline cellulose, ethylcellulose, stearic acid. The pellets are manufactured by extruding and spheronizing.

[0012] WO2006/061697A1 discloses once a day sustained release granules obtained by wet granulation comprising: a) gliclazide, b) the hydrophilic polymer HPMC K4M and c) HPMC K100VL. The granules are further blended with talc, colloidal silico dioxide and magnesium stearate before compression into tablets.

45 Summary of the invention

[0013] It has now surprisingly been established that gliclazide can be mixed with hydrophilic ingredients in combination with a hydroxypropyl methylcellulose and lipophilic ingredients with a low melting point to obtain dust-free granules suitable, without further handling, for compression to form tablets.

50 **[0014]** Said tablets are characterised in that they release the active ingredients they contain over a period of 24 hours.

Detailed description of the invention

55 **[0015]** Object of the present invention are tablets according to claim 1 and a process for preparing tablets according to claim 8. Oral formulations comprising gliclazide can be mixed with hydrophilic ingredients in combination with a hydroxypropyl methylcellulose and lipophilic ingredients with a low melting point.

[0016] The term hydrophilic ingredients is used to mean hydrophilic polymers (e.g. hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, ethylene polyoxide, carbomer or mixtures thereof), mannitol, dibasic

sodium phosphate, sorbitol, isomalt, or mixtures thereof.

[0017] According to the invention, HPMC is the preferred hydroxypropyl methylcellulose, in a solution at 2% w/w, with a viscosity corresponding to approximately 4000 cps. The term lipophilic elements with a low melting point is used herein to mean, for instance, stearic acid, carnauba wax, cetyl alcohol or cetyl stearyl alcohol. According to the invention, the above-mentioned components are contained in the following proportions (calculated weight to weight with respect to the total weight of the mixture):

[0018]

10	Gliclazide:	10-30%
	Stearic acid	5-20%
	Carnauba wax	5-20%
	HPMC (viscosity 2% w/w approx 4000 cps)	5-25%
	Mannitol	10-50%
15	Dibasic sodium phosphate	10-30%
	Magnesium stearate	0.1-5%
	Anhydrous colloidal silica	0.1-5%
	HPMC 5 cps	1 - 5%
	PEG 4000	0.1 - 5%
20	Talc	0.1-5%
	Titanium dioxide	0.1 - 5%

[0019] More preferably:

25	Gliclazide:	15-20%
	Stearic acid	10-20%
	Carnauba wax	5-15%
	HPMC (viscosity 2% w/w approx 4000 cps)	10-20%
30	Mannitol	15-40%
	Dibasic sodium phosphate	10-20%
	Magnesium stearate	1-3%
	Anhydrous colloidal silica	1-3%
35	HPMC 5 cps	1-4%
	PEG 4000	0.1-3%
	Talc	0.5-3%
	Titanium dioxide	0.5-4%

[0020] The above-described granules can be prepared in a single production step by granulation-extrusion at a temperature lower than 50°C, using standard granule production methods.

[0021] The granules are then mixed with the typical additives used in the preparation of tablets for oral administration, such as:

45	lubricants	0.5-2%
	separating agents	0.1-3%
	anticaking agents	0.1-10%

and ultimately compressed.

[0022] If necessary, the tablets are subsequently coated with a soluble film (generally containing a low-viscosity hydroxypropyl methylcellulose or acrylic polymers, or colouring agents, etc) to facilitate their swallowing, make the tablets readily identifiable and facilitate subsequent procedures.

[0023] For the sake of completeness and a better understanding of the present invention, several examples of formulations according to the invention and their preparation are given below.

Example 1

[0024] The components listed below are mixed together in an automatic drum mixer for 20 minutes at a turning speed of 4 rpm.

5	Gliclazide	3000 g (19.5%)
	Mannitol	4481 g (29.1%)
	Stearic acid	1539 g (10.0%)
10	Carnauba wax	1539 g (10.0%)
	Dibasic sodium phosphate	2923 g (19.0%)
	HPMC (viscosity 2% w/w approx 4000 cps)	1904 g (12.4%)

[0025] The resulting mixture is extruded using the Leistritz HP18 extruder in the following working conditions:

15	temperature of the refrigerant:	15°C
	temperature of the extruder:	50°C
	temperature of the extruded products:	53°C

[0026] The granules thus obtained are mixed with the lubricants (magnesium stearate and anhydrous colloidal silica) and compressed into tablets containing doses of 30 and 60 mg of active ingredient.

20	Magnesium stearate:	2 mg/tab (30 mg)	4mg/cpr (60 mg)
25	Anhydrous colloidal silica:	1 mg/tab (30 mg)	2 mg/tab (60 mg)

[0027] Characteristics of the tablets:

30	mean weight of tablet:	157 mg
	shape of tablet:	oval
	size of tablet:	11x5.6 mm

[0028] The tablets thus obtained are coated with a film in a GS 25 drum mixer using a titanium-dioxide-based white colouring agent in order to obtain a 10 mg increase in the weight of the tablet, under the following working conditions:

35	air temperature at inlet:	55°C
	drum turning speed:	12 rpm
40	nebulising pressure:	1 bar

[0029] The resulting tablets have a 24-hour release profile.

Example 2

[0030] The components listed below are mixed in a suitable mixer:

45	Gliclazide	733 g	(19,5%)
	Mannitol	1095 g	(29,1%)
50	Stearic acid	376 g	(10.0%)
	Carnauba wax	376 g	(10.0%)
	Dibasic sodium phosphate	714 g	(19.0%)
	HPMC (viscosity 2% w/w approx 4000 cps)	465 g	(12.4%)

[0031] The resulting mixture is extruded using the Leistritz HP18 extruder; the granules obtained are mixed with the lubricants and then compressed into tablets containing 30 and 60 mg of active ingredient, as previously described in example 1.

[0032] The tablets have a 24-hour release profile.

Example 3

[0033] The components listed below are mixed in a suitable mixer.

Gliclazide	733 g	(19.5%)
Isomalt	950 g	(25.3%)
Stearic acid	448 g	(11.9%)
Carnauba wax	449 g	(11.9%)
Dibasic sodium phosphate	700 g	(18.6%)
HPMC (viscosity 2% w/w approx 4000 cps)	479 g	(12.8%)

[0034] The mixture thus obtained is extruded using the Leistritz HP18 extruder; the resulting granules are mixed with the lubricants and subsequently compressed into tablets containing doses of 30 and 60 mg of active ingredient, as described previously in example 1.

[0035] The tablets have a 24-hour release profile.

[0036] As an example, the analytical results obtained on a batch of gliclazide 30 mg are given below.

Time	Release
1 h	16%
4h	55%
8h	86%
12h	100%

Claims

1. Tablets comprising granules consisting of:

Gliclazide:	10-30%
Stearic acid	5-20%
Carnauba wax	5-20%
HPMC (viscosity 2% w/w approx 4000 cps)	5-25%
Mannitol	10-50%
Dibasic sodium phosphate	10-30%
Magnesium stearate	0.1-5%
Anhydrous colloidal silica	0.1-5%
HPMC 5 cps	1 - 5%
PEG 4000	0.1 - 5%
Talc	0.1 - 5%

wherein the granules are granulated extruded in a single production step at a temperature below 50°C, using standard granule production methods.

2. Tablets according to claim 1, wherein the granules are consisting of:

Gliclazide:	15-20%
Stearic acid	10-20%
Carnauba wax	5-15%
HPMC (viscosity 2% w/w approx 4000 cps)	10-20%
Mannitol	15-40%
Dibasic sodium phosphate	10-20%

(continued)

	Magnesium stearate	1-3%
	Anhydrous colloidal silica	1-3%
5	HPMC 5 cps	1-4%
	PEG 4000	0.1-3%
	Talc	0.5-3%
	Titanium dioxide	0.5-4%

10 3. Tablets according to any of claims 1-2 wherein the granules are consisting of:

	Gliclazide	19.5%
15	Mannitol	29.1%
	Stearic acid	10.0%
	Carnauba wax	10.0%
	Dibasic sodium phosphate	19.0%
	HPMC (viscosity 2% w/w approx 4000 cps)	12.4%; or
20	Gliclazide	19.5%
	Isomalt	25.3%
	Stearic acid	11.9%
	Carnauba wax	11.9%
25	Dibasic sodium phosphate	18.6%
	HPMC (viscosity 2% w/w approx 4000 cps)	12.8%

4. Tablets according to any of claims 1-3, comprising the granules in combination with additives chosen from among the following:

	lubricants	0.5-2%
	separating agents	0.1-3%
35	anticaking agents	0.1-10%

5. Tablets according to claim 4, coated with a soluble film.

6. Tablets according to claim 4 comprising granules according to claim 3, in combination with magnesium stearate and anhydrous colloidal silica.

7. Tablets according to claim 6, coated with a soluble and/or colouring film.

8. A process for preparing tablets according to any of claims 1-7, said process comprising
 45 preparing granules as defined in any of claims 1 -5 by a single production step of granulation-extrusion at a temperature below 50°C, using standard methods for the production of granules
 the granules are then mixed with the typical additives used in the preparation of tablets for oral administration and ultimately compressed.

Patentansprüche

1. Tabletten aufweisend Granulat bestehend aus:

55	Gliclazid:	10 - 30%
	Stearinsäure	5 - 20%
	Carnaubawachs	5 - 20%

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(fortgesetzt)

	HPMC (Viskosität 2 Gew.-% ca. 4000 cps)	5 - 25%
	Mannitol	10 - 50%
5	Zweibasisches Natriumphosphat	10 - 30%
	Magnesiumstearat	0,1 - 5%
	Wasserfreie kolloidale Siliziumdioxid	0,1 - 5%
	HPMC 5 cps	1 - 5%
10	PEG 4000	0,1 - 5%
	Talkum	0,1 - 5%

wobei das Granulat in einem einzigen Produktionsschritt bei einer Temperatur von unter 50 °C unter Verwendung von Standardverfahren zur Herstellung von Granulat granuliert und extrudiert wird.

15

2. Tabletten nach Anspruch 1, wobei das Granulat aus folgenden Bestandteilen besteht:

	Gliclazid:	15 - 20%
20	Stearinsäure	10 - 20%
	Carnaubawachs	5 - 15%
	HPMC (Viskosität 2 Gew.-% ca. 4000 cps)	10 - 20%
	Mannitol	15 - 40%
	Zweibasisches Natriumphosphat	10 - 20%
25	Magnesiumstearat	1 - 3%
	Wasserfreie kolloidale Siliziumdioxid	1 - 3%
	HPMC 5 cps	1 - 4%
	PEG 4000	0,1 - 3%
30	Talkum	0,5 - 3%
	Titaniumdioxid	0,5 - 4%

3. Tabletten nach einem der Ansprüche 1 bis 2, wobei das Granulat aus folgenden Bestandteilen besteht

35

	Gliclazid	19,5%
	Mannitol	29,1%
	Stearinsäure	10,0%
40	Carnaubawachs	10,0%
	Zweibasisches Natriumphosphat	19,0%
	HPMC (Viskosität 2 Gew.-% ca. 4000 cps)	12,4 %; oder
	Gliclazid	19,5 %
	Isomalt	25,3 %
45	Stearinsäure	11,9 %
	Carnaubawachs	11,9 %
	Zweibasisches Natriumphosphat	18,6 %
	HPMC (Viskosität 2 Gew.-% ca. 4000 cps)	12,8 %

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4. Tabletten nach einem der Ansprüche 1 bis 3, aufweisend das Granulat in Kombination mit Zusatzstoffen, die aus den folgenden ausgewählt sind:

55	Gleitmittel	0,5 - 2%
	Trennmittel	0,1 - 3%
	Antibackmittel	0,1 - 10%

5. Tabletten nach Anspruch 4, überzogen mit einem löslichen Film.
6. Tabletten nach Anspruch 4, aufweisend Granulat nach Anspruch 3 in Kombination mit Magnesiumstearat und wasserfreiem kolloidalem Siliciumdioxid.
7. Tabletten nach Anspruch 6, beschichtet mit einem löslichen und/oder färbenden Film.
8. Verfahren zur Herstellung von Tabletten nach einem der Ansprüche 1 bis 7, wobei das Verfahren umfasst Herstellung eines Granulats nach einem der Ansprüche 1 bis 5 durch einen einzigen Produktionsschritt der Granulationsextrusion bei einer Temperatur unter 50 °C unter Verwendung von Standardverfahren zur Herstellung von Granulaten das Granulat wird dann mit den typischen Zusatzstoffen für die Herstellung von Tabletten zur oralen Einnahme vermischt und schließlich gepresst.

Revendications

1. Comprimés comprenant des granulés constitués de :

Gliclazide :	10 à 30 %
Acide stéarique	5 à 20 %
Cire de carnauba	5 à 20 %
HPMC (viscosité 2 % p/p environ 4000 cps)	5 à 25 %
Mannitol	10 à 50 %
Phosphate de sodium dibasique	10 à 30 %
Stéarate de magnésium	0,1 à 5 %
Silice colloïdale anhydre	0,1 à 5 %
HPMC 5 cps	1 à 5 %
PEG 4000	0,1 à 5 %
Talc	0,1 à 5 %

dans lesquels les granulés sont extrudés en une seule étape de production à une température inférieure à 50 °C, en utilisant des méthodes standard de production de granulés.

2. Comprimés selon la revendication 1, dans lesquels les granulés sont constitués de :

Gliclazide :	15 à 20 %
Acide stéarique	10 à 20 %
Cire de carnauba	5 à 15 %
HPMC (viscosité 2 % p/p environ 4000 cps)	10 à 20 %
Mannitol	15 à 40 %
Phosphate de sodium dibasique	10 à 20 %
Stéarate de magnésium	1 à 3 %
Silice colloïdale anhydre	1 à 3 %
HPMC 5 cps	1 à 4 %
PEG 4000	0,1 à 3 %
Talc	0,5 à 3 %
Dioxyde de titane	0,5 à 4 %

3. Comprimés selon l'une quelconque des revendications 1 à 2 dans lesquels les granulés sont constitués de :

Gliclazide	19,5 %
Mannitol	29,1 %

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(suite)

5	Acide stéarique	10,0 %
	Cire de carnauba	10,0 %
	Phosphate de sodium dibasique	19,0 %
	HPMC (viscosité 2 % p/p environ 4000 cps)	12,4 % ; ou
	Gliclazide	19,5 %
10	Isomalt	25,3 %
	Acide stéarique	11,9 %
	Cire de carnauba	11,9 %
	Phosphate de sodium dibasique	18,6 %
	HPMC (viscosité 2 % p/p environ 4000 cps)	12,8 %

- 15 4. Comprimés selon l'une quelconque des revendications 1 à 3, comprenant les granulés en combinaison avec des additifs choisis parmi les suivants :

20	lubrifiants	0,5 à 2 %
	agents de séparation	0,1 à 3 %
	agents anti-mottant	0,1 à 10 %

5. Comprimés selon la revendication 4, enrobés d'un film soluble.

- 25 6. Comprimés selon la revendication 4 comprenant des granulés selon la revendication 3, en combinaison avec du stéarate de magnésium et de la silice colloïdale anhydre.

7. Comprimés selon la revendication 6, enrobés d'un film soluble et/ou colorant.

- 30 8. Procédé de préparation de comprimés selon l'une quelconque des revendications 1 à 7, ledit procédé comprenant

préparer des granulés tels que définis dans l'une quelconque des revendications 1 à 5 en une seule étape de production de granulation-extrusion à une température inférieure à 50 °C, en utilisant des méthodes standard pour la production de granulés
35 les granulés sont ensuite mélangés avec les additifs typiques utilisés dans la préparation de comprimés pour l'administration orale et enfin comprimés.

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REFERENCES CITED IN THE DESCRIPTION

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- WO 2006061697 A1 [0012]

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