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(54) Valsartan formulations

Valsartanformulierungen

Formulations de valsartan

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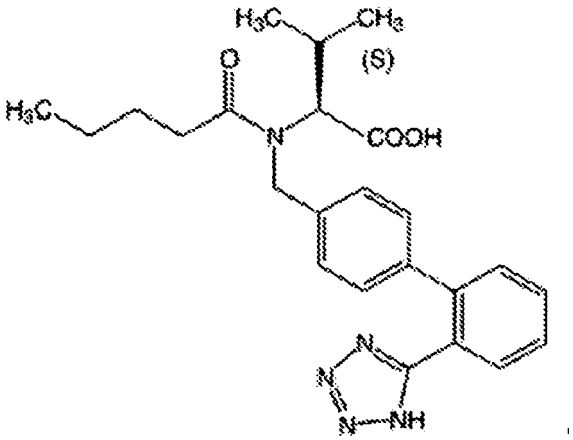
Description

[0001] The present invention relates to a new pharmaceutical formulation in the form of a tablet consisting of valsartan as an active agent, pregelatinized starch, microcrystalline cellulose.

Background of the invention

[0002] Valsartan, a compound having the chemical name N-(1-oxopentyl)-N-[[2'-(1h-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-L-valine, of formula I;



Formula I

[0003] Valsartan belongs to the group of drugs that block receptors of angiotensin II and thus cause a decrease of blood pressure. Presently valsartan tablets are marketed by Novartis as DIOVAN® in doses of 40, 80, 160 and 320 mg and it is used to treat hypertension.

[0004] WO 9524901 A1 (CIBA-GEIGY AG) 07.03.1995, page 6 is directed to the use of valsartan for the treatment of diabetic nephropathy. A hard gelatine capsule comprising valsartan is disclosed.

[0005] In the international patent application WO 9524901 A1 (CIBA-GEIGY AG) 07.03.1995, example 1, a dosage capsule form is described of the following composition:

Valsartan	80.0 mg
Microcrystalline cellulose	110.0 mg
Polyvidone K30	45.2 mg
Sodium lauryl sulphate	1.2 mg
Crospovidone	26.0 mg
Magnesium Stearate	2.6 mg

[0006] The described capsule dosage form above is prepared by below method. Valsartan and microcrystalline cellulose are granulated via wet granulation with solution of polyvidone and sodium lauryl sulphate in water. The granules are dried. Crospovidone and magnesium stearate are added to the dry granulate and the mixture is filled into capsules.

[0007] WO 9749394 A2 (NOVARTIS AG) 18.06.1997, page 14, example 1:

Valsartan	80.0 mg
HCTZ	12.5 mg
Aerosil	1.5 mg
Microcrystalline cellulose	31.5 mg
Crospovidone	20.0 mg
Magnesium Stearate	4.5 mg

[0008] The first fifth components above formulation are mixed and compacted at pressures 25 to 65 kN. The compacted

material is further forced through a sieve. Granulate produced in this way is mixed with magnesium stearate and the mixture is compressed into tablets.

[0009] What is considered an extraordinary advantage of the production method of the cited application is the fact that for each specific formulation it is possible to find minimal necessary compacting pressure within the range of compacting pressures from 25 up to 65 kN, which results in obtaining a tablet having about six times faster disintegration rate than that obtained via usual compacting (i.e. using higher pressure).

[0010] WO 9749394 A2 (NOVARTIS AG) 18.06.1997, discloses compressed solid oral dosage forms, e.g., by compaction of valsartan (optionally in salt form) optionally

[0011] combined with HCTZ. In this application, the preferred range of cellulose is given 10 to 30%, e.g., 21%, for valsartan/HCTZ compositions and 5% valsartan alone. The preferred range of crospovidone is given as 10 to 20%, e.g., 13%.WO 0038676 A1 (NOVARTIS AG) 22.12.1999, page 24, lines 23-30 the application relates to a solid oral dosage form comprising valsartan as the active agent and microcrystalline cellulose wherein the weight ratio of valsartan to microcrystalline cellulose is from 2.5:1 to 0.3:1, e.g., 2:1 to 1:1, e.g., 1.4:1. This application relates to a solid oral dosage form comprising valsartan as the active agent and more than 30% of microcrystalline cellulose by weight based on the total weight of the core components of said solid oral dosage form e.g., 31 to 65%, e.g., 50%.

[0012] WO 0038676 A1 page 24, lines 15-21 it has been found surprisingly that it is possible to improve the bioavailability characteristics of known solid formulations of valsartan by increasing the proportion of microcrystalline cellulose. It has also been found surprisingly that it is possible to improve the quality, e.g., better weight uniformity and better compression for the tablets, of said known solid formulations of valsartan by decreasing proportion of crosslinked PVP.
In further aspect, this application relates to a solid oral dosage form comprising valsartan as the active agent and microcrystalline cellulose wherein the weight ratio of valsartan to microcrystalline cellulose is from 2.5:1 to 0.3:1, e.g., 2:1 to 1:1, e.g., 1.4:1

[0013] WO 2005041941 A2 (ZENTIVA A.S.) 02.11.2004, page 5, lines 26-32 and page 6, lines 1-5 the tablet material described in this application includes, apart from the valsartan active substance, optionally valsartan in combination with HCTZ, other additives, of which the most important one is suitably selected filler, which has a decisive importance for quality of the produced tablets. For ensuring the function of direct tabletting it is necessary to select filler having a defined particle size and in defined amount.

[0014] A preferable composition of the filler according to the invention WO 2005041941 A2 is microcrystalline cellulose having a particle size of 10 to 1000μm, preferably 50 to 190μm, especially preferably 90μm, in amounts above 40 to 60% by weight, spray-dried anhydrous lactose having a particle size of 10 to 250μm, preferably 150 to 250μm, in amounts of 30 to 60%, compact lactose hydrate having particle size of 10 to 250μm, in amounts 40 to 60% by weight, a polyalcohol selected from mannitol or sorbitol, which is compacted and has a particle size of 100 to 850μm, preferably 200 to 400 μm, in amounts of 40 to 60% by weight, calcium hydrogen phosphate having particle size of 10 to 200μm in amounts of 40 to 60% by weight, a combination of microcrystalline cellulose with lactose, preferably spray-dried anhydrous lactose, in a weight ratio of 1:2 to 2:1 in amounts of 20 to 55%, and a combination of microcrystalline cellulose and a polyalcohol, preferably a compacted polyalcohol, in a ratio of 1:2, in amounts of 20 to 55%, based on the total weight of the formulation.

Summary of the Invention

[0015] Objective of the present invention is to create a tablet containing valsartan as active ingredient, which has high powder flowability and easily divided into two or more pieces while being stable enough for transport and commercial use and that resists humidity for several days without taking up moisture or breaking apart if unblistered.

Description of the Invention

[0016] Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water. In state of the art valsartan is micronized to obtain better dissolution. This process causes flowability problem in manufacturing. While in the state of the art tablets are known, said tablets have several disadvantages. Normally those tablets are very porous and thus not very hard. As a consequence they cannot be broken into two or more pieces, which renders them useless for regiments wherein only one half of a tablet shall be taken at a time. Additionally these porous tablets tend to be very sensitive to humidity. As a consequence they can not be stored for some days once the blister is opened.

[0017] It has been found surprisingly that it is possible to improve physical stability of valsartan formulation by reducing the water activity of the formula by using microcrystalline cellulose and pregelatinized starch weight ratio. It has been also found surprisingly that it is possible to improve the flowability characteristics of known solid formulations of valsartan by increasing the proportion of microcrystalline cellulose and pregelatinized starch. A more surprisingly it is possible to improve the resistance to humidity.

[0018] The present invention relates a pharmaceutical formulation in the form of a tablet consisting of ;

- 20 to 34% (w/w) of valsartan as active agent,
- microcrystalline cellulose and pregelatinized starch in a weight ratio of between 1:1 and 5:1,
- colloidal silicon dioxide,
- magnesium stearate

[0019] the tablet being preparable by directly compressing the ingredients at a pressure of 90 N to 270 N.

[0020] In a further embodiment, the tabletting mixture includes substances that improve its flow properties. Microcrystalline cellulose and pregelatinized starch are the most advantageous substance for the described mixture in this invention; preferably in a weight ratio of microcrystalline cellulose to pregelatinized starch is from 1 to 5. This ratio is calculated by dividing the weight of microcrystalline cellulose to the weight of pregelatinized starch. Ratio of these substances is important for avoiding fluctuations of the tablet weight, caused by inappropriate flow of the solid mixture through the hopper into the high performance tabletting machine.

[0021] The tablet has 80 mg to 320 mg valsartan. The tablet contains one or more filling and/or disintegrating agents. These agents are useful to produce tablets of a certain size and to support flowability step. The filling and/or disintegrating agents are microcrystalline cellulose and pregelatinized starch. The tablet also contains one or more lubricant or glidant. Lubricants and glidants are well known in the state of the art. Among them, the lubricant(s) are selected from the group of stearate, preferably magnesium stearate. The glidant(s) are selected from the group of silicon dioxide, preferably colloidal silicon dioxide.

[0022] In a further aspect, invention relates a pharmaceutical formulation in the form of a tablet consisting of;
20 to 34% of valsartan
40 to 60% of microcrystalline cellulose
8 to 40% of pregelatinized starch
0.5 to 1.5% of colloidal silicon dioxide
1.5 to 4.0% of magnesium stearate.

[0023] The tablets that described in examples are produced by direct compression techniques. Firstly, valsartan, microcrystalline cellulose, pregelatinized starch are mixed. Colloidal silicon dioxide are added to this powder and mixed. Then magnesium stearate are added to this powder and mixed. Finally, mixture is compressed by tablet compression machine.

[0024] In a further aspect, the present invention relates to tablet comprising valsartan as the active agent, microcrystalline cellulose and pregelatinized starch wherein the weight ratio of microcrystalline cellulose to pregelatinized starch is from 1 to 5.

[0025] To overcome the flowability problem and sensitivity to humidity of valsartan the tablets have high microcrystalline cellulose and pregelatinized starch rate.

Example 1

[0026]

(MCC: PS=5.0: 1)	
Valsartan	80.0 mg
Microcrystalline cellulose (MCC)	175.0 mg
Pregelatinized starch (PS)	35.0 mg
Colloidal silicon dioxide	2.5 mg
Magnesium stearate	7.0 mg
	299.5 mg

Example 2

[0027]

(MCC: PS=3.5:1)	
Valsartan	80.0 mg
Microcrystalline cellulose (MCC)	125.0 mg
Pregelatinized starch (PS)	35.5 mg
Colloidal silicon dioxide	2.5 mg
Magnesium stearate	7.0 mg

(continued)

	250.0 mg

Example 3

[0028]

(MCC: PS=1:1)	
Valsartan	80.0 mg
Microcrystalline cellulose (MCC)	42.0 mg
Pregelatinized starch (PS)	42.0 mg
Colloidal silicon dioxide	2.5 mg
Magnesium stearate	7.5 mg
	174.0 mg

Example 4

[0029]

(MCC: PS=4.5:1)	
Valsartan	160.0 mg
Microcrystalline cellulose (MCC)	315.0 mg
Pregelatinized starch (PS)	70.0 mg
Colloidal silicon dioxide	5.0 mg
Magnesium stearate	14.0 mg
	564.0 mg

Example 5

[0030]

(MCC: PS=3.5:1)	
Valsartan	160.0 mg
Microcrystalline cellulose (MCC)	250.0 mg
Pregelatinized starch (PS)	71.0 mg
Colloidal silicon dioxide	5.0 mg
Magnesium stearate	14.0 mg
	500.0 mg

Example 6

[0031]

(MCC: PS=2.5:1)	
Valsartan	160.0 mg
Microcrystalline cellulose (MCC)	210.0 mg
Pregelatinized starch (PS)	84.0 mg
Colloidal silicon dioxide	5.0 mg
Magnesium stearate	15.0 mg
	474.0 mg

Example 7

[0032]

(MCC: PS=2.5:1)	
Valsartan	320.0 mg
Microcrystalline cellulose (MCC)	420.0 mg
Pregelatinized starch (PS)	168.0 mg
Colloidal silicon dioxide	10.0 mg
Magnesium stearate	30.0 mg
	948.0 mg

[0033] Above formulations containing pregelatinized starch and microcrystalline cellulose show improved physical stability in this formulation due to its ability to reduce the water activity of the formula. In addition to these benefits, the results would show the strong flow functionality of pregelatinized starch and microcrystalline cellulose.

[0034] After exhaustive testing it has been found surprisingly that it is possible to improve the flowability characteristics of known solid formulations of valsartan by increasing the proportion of microcrystalline cellulose and pregelatinized starch. It has also been found surprisingly that it is possible to improve the resistance to humidity. (Table 1)

Table 1. Loss on Drying Results Of Stability

Example No	Valsartan amount (mg)	MCC: PS	Loss on Drying % (3 month stability)	Loss on Drying % (6 month stability)
1	80	5.0	0.8	1.2
			0.6	0.9
2	80	3.5	1.0	1.3
			1.2	1.5
3	80	1.0	2.1	2.3
			2.5	2.6
4	160	4.5	1.3	1.5
			1.4	1.7
5	160	3.5	1.6	1.9
			2.3	2.7
6	160	2.5	2.0	2.0
			2.8	3.0
7	320	2.5	2.9	3.1
			2.7	3.2

Claims

1. A pharmaceutical formulation in the form of a tablet consisting of

- 20 to 34% (w/w) of valsartan as active agent,
- microcrystalline cellulose and pregelatinized starch in a weight ratio of between 1:1 and 5:1,
- colloidal silicon dioxide,
- magnesium stearate

the tablet being preparable by directly compressing the ingredients at a pressure of 90 N to 270 N.

2. The tablet according to claim 1 wherein the valsartan is present in an amount of between 80 and 320 mg of valsartan.

3. The tablet according to claim 1 consisting of;
20 to 34% of valsartan
40 to 60% of microcrystalline cellulose
8 to 40% of pregelatinized starch
0.5 to 1.5% of colloidal silicon dioxide
1.5 to 4.0% of magnesium stearate.

Patentansprüche

1. Pharmazeutische Zubereitung in der Form einer Tablette bestehend aus

- 20 bis 34% (w/w) Valsartan als aktivem Wirkstoff,
- mikrokristalliner Cellulose und modifizierter Stärke in einem Gewichtsverhältnis zwischen 1:1 und 5:1,
- kolloidalem Siliziumdioxid,
- Magnesiumstearat,

wobei die Tablette durch Direkttablettierung der Bestandteile bei einem Druck von 90 N bis 270 N hergestellt ist.

2. Tablette nach Anspruch 1, in der das Valsartan in einer Menge zwischen 80 und 320 mg Valsartan vorhanden ist.

3. Tablette nach Anspruch 1, bestehend aus:

20 bis 34% Valsartan
40 bis 60% mikrokristalliner Cellulose
8 bis 40% modifizierter Stärke
0,5 bis 1,5% kolloidalem Siliziumdioxid
1,5 bis 4,0% Magnesiumstearat.

Revendications

1. Formulation pharmaceutique sous forme de comprimé constitué de

- 20 à 34 % (p/p) de valsartan en tant que principe actif,
- de la cellulose microcristalline et de l'amidon prégélatinisé dans un rapport pondéral compris entre 1:1 et 5:1,
- du dioxyde de silicium colloïdal,
- du stéarate de magnésium,

le comprimé pouvant être préparé par compression directe des composants à une pression de 90 N à 270 N.

2. Comprimé selon la revendication 1 où le valsartan est présent en une quantité comprise entre 80 et 320 g de valsartan.

3. Comprimé selon la revendication 1 constitué de
20 à 34 % de valsartan
40 à 60 % de cellulose microcristalline
8 à 40 % d'amidon prégélatinisé
0,5 à 1,5 % de dioxyde de silicium colloïdal
1,5 à 4,0 % de stéarate de magnésium.

REFERENCES CITED IN THE DESCRIPTION

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- WO 9749394 A2 **[0007] [0010]**
- WO 0038676 A1 **[0011] [0012]**
- WO 2005041941 A2 **[0013] [0014]**