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An agency of Industry Canada

CA 2259148 C 2009/09/29

(11)(21) 2 259 148

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 1997/06/18
(87) Date publication PCT/PCT Publication Date: 1997/12/31
(45) Date de délivrance/Issue Date: 2009/09/29
(85) Entrée phase nationale/National Entry: 1998/12/16
(86) N° demande PCT/PCT Application No.: EP 1997/003172
(87) N° publication PCT/PCT Publication No.: 1997/049394
(30) Priorité/Priority: 1996/06/27 (GB9613470.5)

(51) Cl.Int./Int.Cl. *A61K 31/41* (2006.01), *A61K 31/54* (2006.01), *A61K 9/16* (2006.01), *A61K 9/20* (2006.01)

(72) Inventeurs/Inventors:
WAGNER, ROBERT FRANK, US;
KATAKUSE, YOSHIMITSU, JP;
TAIKE, TAKASHI, JP;
YAMATO, FUJIKI, JP;
KOHLMEYER, MANFRED, CH

(73) Propriétaire/Owner:
NOVARTIS AG, CH

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : FORMES POSOLOGIQUES SOLIDES DE VALSARTAN ADMINISTREES PAR VOIE ORALE
(54) Title: SOLID ORAL DOSAGE FORMS OF VALSARTAN

(57) Abrégé/Abstract:
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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/41, 9/16, 9/20

A2

(11) International Publication Number: **WO 97/49394**

(43) International Publication Date: 31 December 1997 (31.12.97)

(21) International Application Number: PCT/EP97/03172

(22) International Filing Date: 18 June 1997 (18.06.97)

(30) Priority Data:
9613470.5 27 June 1996 (27.06.96) GB

(71) Applicant *(for all designated States except US)*: NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: WAGNER, Robert, Frank [US/US]; 1 Cedarview Court, Neshanic Station, NJ 08853 (US). KATAKUSE, Yoshimitsu [JP/JP]; 1-9-20, Hoshigaoka, Hirakata 573 (JP). TAIKE, Takashi [JP/JP]; 2-7-3, Shoubugaoka, Kitaku, Kobe 651-13 (JP). YAMATO, Fujiki [JP/JP]; 3-5-504, Komyo-cho, Takarazuka 665 (JP). KOHLMEYER, Manfred [DE/CH]; Bläsiring 47, CH-4057 Basel (CH).

(74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

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(57) Abstract

The present invention is concerned with solid oral dosage forms comprising of a) an active agent selected from valsartan and optionally HCTZ, and b) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods.

SOLID ORAL DOSAGE FORMS OF VALSARTAN

The invention relates to solid oral dosage forms containing valsartan, in particular solid oral dosage forms containing valsartan and hydrochlorothiazide (HCTZ) and a process of forming the same.

The angiotensin II receptor antagonist - Valsartan - is known to be effective in the treatment of congestive heart failure and reducing blood pressure irrespective of age, sex or race and is also well tolerated. Its combination with HCTZ is also known for the treatment of hypertension.

The oral administration of such pharmaceutical agents as tablets or capsules has certain advantages over parenteral administration such as i.v. or i.m.: Diseases requiring treatment with painful injectable formulations are considered to be more serious than those conditions which can be treated with oral dosage forms. However, the major advantage with oral formulations is held to be their suitability for self administration whereas parenteral formulations have to be administered in most cases by a physician or paramedical personnel.

However, valsartan is difficult to formulate and heretofore it has not been possible to make oral formulations in the form of tablets in a reliable and robust way.

Capsules are undesirable since large capsules must be used to accommodate effective amounts of active agent, which in the case of valsartan, is of low density and is therefore rather bulky.

We have now found a solid oral dosage form containing valsartan or a pharmaceutically acceptable salt thereof optionally in combination with HCTZ which can be produced according to a reliable and robust process, which solid oral dosage form is small relative to the amount of active agent used. Said solid oral dosage forms are smaller, for a given amount of active agent, than any known formulations of this active substance.

According to the invention, there is provided a solid oral dosage form comprising

a) an active agent containing an effective amount of valsartan or a pharmaceutically acceptable salt thereof and

b) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods

preferably wherein the active agent is present in an amount of more than 35 % by weight, preferably more than 50 % by weight based on the total weight of the solid oral dosage form. In particular, the amount of active agent may be present in an amount of from 45 to 65 % by weight, e.g. 57 to 62 % by weight.

According to one aspect of the present invention, there is provided a compressed solid dosage form comprising a) valsartan or a pharmaceutically acceptable salt thereof; and, b) at least one pharmaceutically acceptable additive wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 35% by weight based on the total weight of the compressed solid dosage form.

According to another aspect of the present invention, there is provided a compressed solid dosage form which comprises valsartan or a pharmaceutically acceptable salt thereof; HCTZ; and, at least one pharmaceutically acceptable additive; wherein the valsartan or the pharmaceutically acceptable salt thereof and the HCTZ are present in an amount of more than 35% by weight based on the total weight of the compressed solid dosage form.

According to yet another aspect of the present invention, there is provided a compressed solid dosage form described herein for treating hypertension, congestive heart failure, angina, myocardial infarction, arteriosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, stroke, left ventricular hypertrophy, cognitive dysfunction, headache, or chronic heart failure.

According to still another aspect of the present invention, there is provided a process of forming a compressed solid dosage form comprising more than 35% by weight of valsartan or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable additive wherein the process comprises the steps of: i) blending the valsartan or the salt thereof and the at least one pharmaceutically acceptable additive to form a mixture; ii) subjecting the mixture to compression to form a coprimate; iii) converting the coprimate into a granulate; and, iv) compressing the granulate to form the compressed solid dosage form.

According to a further aspect of the present invention, there is provided a process of forming a compressed solid dosage form comprising more than 35% by weight of valsartan or the pharmaceutically acceptable salt thereof, HCTZ and at least one pharmaceutically acceptable additive wherein the process comprises the steps of: i) blending the valsartan, or the salt thereof, the HCTZ and the at least one pharmaceutically acceptable additive to form a mixture; ii) subjecting the mixture to compression to form a coprimate; iii) converting the coprimate into a granulate; and, iv) compressing the granulate to form the compressed solid dosage form.

According to still a further aspect of the present invention, there is provided a dry-compressed solid oral dosage form comprising (a) valsartan or a pharmaceutically acceptable salt thereof and (b) at least one pharmaceutically acceptable additive; wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 35 % by weight based on the total weight of the compressed solid oral dosage form.

According to another aspect of the present invention, there is provided a process of making a solid oral dosage form comprising a) valsartan or a pharmaceutically acceptable salt thereof and b) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods; wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 35% by weight based on the total weight of the compressed solid oral dosage form; wherein the process comprises the steps of: i) grinding the active agent and pharmaceutically acceptable additives, ii) subjecting a mixture of the ground active agent and additives to compression to form a comprimate, wherein compression to form a comprimate requires the compaction of the dry ground components, iii) converting the comprimate into granulate and iv) compressing the granulate to form the solid oral dosage form.

According to yet another aspect of the present invention, there is provided a compressed tablet comprising a) 80 mg valsartan or a pharmaceutically acceptable salt thereof and b) pharmaceutically acceptable additives suitable for the preparation of compressed tablets; wherein the valsartan or the pharmaceutically acceptable salt

thereof is present in an amount of more than 35% by weight based on total weight of the compressed tablet.

According to still another aspect of the present invention, there is provided a solid oral dosage form comprising a) 160 mg valsartan or a pharmaceutically acceptable salt thereof and b) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods; wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 35% by weight based on total weight of the solid oral dosage form.

Solid oral dosage forms according to the invention provide for the administration of the active substance in a smaller oral form than was heretofore possible for a given unit dose of active agent. Furthermore, the oral dosage forms obtained are stable both to the production process and during storage, e.g. for 2 years in conventional packaging, e.g. sealed aluminium blister packs.

By "effective amount" is meant the amount of active agent which halts or reduces the progress of the condition being treated or which otherwise completely or partly cures or acts palliatively on the condition. Such an amount can be easily determined by a person skilled in the art by routine experimentation and with no undue burden.

In a solid oral dosage form according to the invention wherein the active agent consists entirely of valsartan or a pharmaceutically acceptable salt thereof, it is preferred if the active agent is present in an amount of from 10 to 250 mg, more preferable 40 to 160 mg, most preferably 40 to 80 mg, e.g. 40, 80 or 160 mg.

The active agent valsartan is particularly suitable for combination with other active agents, e.g. HCTZ.

Accordingly, in an further embodiment of the invention there is provided a solid oral dosage form as hereinabove described additionally containing HCTZ as a component of the active agent.

It has been found that valsartan, or a pharmaceutically acceptable salt thereof, combined in a dose range from about 10 to 250 mg with hydrochlorothiazide in a dose range from about 6 to 60 mg, is suitable for more efficient treatment of hypertension. With these dose ranges of the combined active agents, valsartan is found to have a greater efficacy in reducing elevated blood pressure to normal levels than it would have if used at the same dose range in monotherapy. Moreover, when hydrochlorothiazide is being administered in combination with valsartan, the diuretic agent is more effective as compared to monotherapy at the dose range indicated. Particularly suitable is a dose range from about 50 and 100 mg valsartan or a pharmaceutically acceptable salt thereof and from about 10 to 30 mg hydrochlorothiazide. More preferred is a unit dose of about 80 mg valsartan and 12.5 mg or 25 mg of hydrochlorothiazide and 160 mg valsartan and 12.5 mg or 25 mg of hydrochlorothiazide. The weight ratio of valsartan or a pharmaceutically acceptable salt thereof to hydrochlorothiazide is from about 1:6 to about 42:1, more preferably 2:1 to 13:1, most preferably 2:1 to 10:1.

The present invention particularly relates to a solid oral dosage form, which contain as the active agent a)

a unit dose between about 10 and 250 mg, especially between about 50 and 100 mg, of valsartan or a pharmaceutically acceptable salt thereof; and

a unit dose between about 6 and 60 mg, especially between about 10 and 30 mg, of hydrochlorothiazide.

An especially preferred embodiment of the invention is a solid oral dosage form, which contain as the active agent a)

a unit dose of about 80 mg or 160 mg of valsartan or a pharmaceutically acceptable salt thereof; and

a unit dose of about 12.5 mg hydrochlorothiazide.

The preparation of valsartan is described in the U.S. patent specification no. 5 399 578. A pharmaceutically acceptable salt of
valsartan can be prepared in a manner known per se. Thus for example, acid addition salts are obtained by treatment with an acid or a suitable ion exchange agent. Such salts can be converted to free acid in a conventional manner by treatment with a suitable basic agent.

Valsartan is preferably in its free form, that is, not in one of its salt forms.

Hydrochlorothiazide is a known therapeutic agent which is useful in the treatment of hypertension.

A solid oral dosage form according to the invention comprises additives conventional in the dosage form in question. Tabletting aids, commonly used in tablet formulation can be used and reference is made to the extensive literature on the subject, see in particular Fiedler's "Lexicon der Hilfstoffe", 4th Edition, ECV Aulendorf 1996. These include but are not limited to
disintegrants, binders, lubricants, glidants, stabilising agents, fillers or diluents, surfactants and the like.

As disintegrants one can particularly mention CMC-Ca, CMC-Na, crosslinked PVP (Crospovidone, Polyplasdone of Kollidon XL), Alginic acid, sodium alginate and guar gum, most preferably crosslinked PVP, Crospovidone, crosslinked CMC and Ac-Di-Sol.

As binders one can particularly mention starches, e.g. potato starch, wheat starch, corn starch, microcrystalline cellulose, e.g. products known under the registered trade marks Avicel, Filtrak, Heweten or Pharmacel, hydroxypropyl cellulose, hydroxyethyl cellulose and hydroxypropylmethyl cellulose, e.g. hydroxypropyl cellulose having a hydroxypropyl content of 5 to 16 % by weight and a Mw of from 80 000 to 1 150 000, more particularly 140 000 to 850 000.

As glidants one can mention in particular colloidal silica, e.g. Aerosil , magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

As fillers or diluents one can mention confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, lactose, mannitol, microcellulose, in particular having a density of about 0.45g/cm^3, e.g. Avicel, powdered cellulose, sorbitol, sucrose and talc.

As lubricants one can mention in particular Mg, Al or Ca stearate, PEG 4000 - 8000 and talc.

One or more of these additives can be selected and used by the skilled artisan having regard to the particular desired properties of the solid oral dosage form by routine experimentation and without any undue burden.

The amount of each type of additive employed, e.g. glidant, binder, disintegrant, filler or diluent and lubricant may vary within ranges conventional in the art. Thus for example, the amount of glidant may vary within a range of from 0.1 to 10% by weight, in particular 0.1 to 5% by weight, e.g. 0.1 to 0.5% by weight; the amount of binder may vary within a range of from about 10 to 45% by weight, e.g. 20 to 30% by weight; the amount of disintegrant may vary within a range of from 2 to 20% by weight, e.g. 15% by weight; the amount of filler or diluent may vary within a range of from 15 to 40% by weight; whereas the amount of lubricant may vary within a range of from 0.1 to 5.0% by weight.

It is a characteristic of the present solid oral dosage forms that they contain only a relatively small amount of additives given the high content of active agent. This enables the production of physically small unit dosage forms. The total amount of additives in a given unit dosage may be about 65 % or less by weight based on the total weight of the solid oral dosage form, more particularly about 50 % or less. Preferably the additive content is in the range of about 35 to 55 % by weight, more particularly 45 to 55 % by weight, e.g. 38 to 43 % by weight.

The absolute amounts of each additive and the amounts relative to other additives is similarly dependent on the desired properties of the solid oral dosage form and may also be chosen by the skilled artisan by routine experimentation without undue burden. For example, the solid oral dosage form may be chosen to exhibit accelerated and/or delayed release of the active agent with or without quantitative control of the release of active agent.

Thus, where accelerated release is desired, e.g. about 90% release within a ten minute, more particularly a five minute period, a disintegrant such as crosslinked polyvinyl pyrrolidone, for example those products known under the registered trade marks Polyplasdone®XL or Kollidon®CL, in particular having a molecular weight in excess of 1 000 000, more particularly having a particle size distribution of less than 400 microns or less than 74 microns, or reactive additives (effervescent mixtures) that effect rapid disintegration of the tablet in the presence of water, for example so-called effervescent tablets that contain an acid in solid form, typically citric acid, which acts in water on a base containing chemically combined carbon dioxide, for example sodium hydrogencarbonate or sodium carbonate, and releases carbon dioxide.

Whereas if delayed release is desired one can employ pellet coating technology, wax matrix systems, polymer matrix tablets or polymer coatings conventional in the art.

Quantitative control of the release of the active agent can be achieved by conventional techniques known in the art. Such dosage forms are known as oral osmotic systems (OROS), coated tablets, matrix tablets, press-coated tablets, multilayer tablets and the like.

In a solid oral dosage form wherein the active agent consist entirely of valsartan or a pharmaceutically acceptable salt thereof, preferred additives are microcrystalline cellulose, hydroxypropylcellulose, carboxymethylcellulose (CMC) or CMC-Ca, Mg, Ca or Al stearate, anhydrous colloidal silica and talc. The amounts of additive employed will depend upon how much active agent is to be used. The stearate, e.g. Mg stearate is preferably employed in amounts of 1.0 to 5.0% by weight, e.g. 1.5% to 3.0 % by weight. Whereas the silica is preferably employed in an amount of from 0.5 to 10% by weight.

In a solid oral dosage form wherein the active agent consists of a combination of both valsartan or a pharmaceutically acceptable salt thereof and HCTZ it is preferred to employ additives selected from any of those additives recited in the previous paragraph and crosslinked polyvinylpyrollidone. The stearate is preferably employed in an amount of from 1 to 5% by weight, e.g. 3%. The cellulose material, e.g. microcrystalline cellulose is preferably present in an amount of 10 to 30%, e.g. 21%. The silica is preferably present in an amount of from 0.5 to 10%, e.g. 1% by weight. The crosslinked polyvinylpyrolidone is preferably present in an amount of from 10 to 20%, e.g. about 13% by weight. Particularly preferred solid oral dosage forms contain as additives microcrystalline cellulose and crosslinked polyvinylpyrrolidone (PVP).

The solid oral dosage forms according to the present invention may be in the form of dragèes in which case the solid oral dosage form is provided with a coating typically a sugar, shellac or other film coating entirely conventional in the art. Attention is drawn to the numerous known methods of coating employed in the art, e.g. spray coating in a fluidized bed, e.g. by the known methods using apparatus available from Aeromatic, Glatt, Wurster or Hüttlin, in a perforated pan by the Accela Cota method, or to the

submerged sword coating method. The additives commonly used in confectioning are employed in such methods.

The solid oral dosage forms of the present invention are useful for lowering the blood pressure, either systolic or diastolic or both. The conditions for which the instant invention is useful include, without limitation, hypertension (whether of the malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type), congestive heart failure, angina (whether stable or unstable), myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction (such as Alzheimer's) and stroke.

The exact dose of active agent and the particular formulation to be adminstered depend on a number of factors, e.g. the condition to be treated, the desired duration of the treatment and the rate of release of the active agent. For example, the amount of the active agent required and the release rate thereof may be determined on the basis of known in vitro or in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

The invention provides in another of its aspects a process of making a solid oral dosage form as hereinabove described. Such solid oral dosage form may be produced by working up components a) and b) defined hereinabove in appropriate amounts, to form unit dosage forms.

In a preferred embodiment there is provided a process of making the solid oral dosage forms as hereinabove described comprising the steps of

i) grinding the active agent and pharmaceutically acceptable additives,

ii) subjecting a mixture of the ground active agent and additives to compression to form a coprimate

iii) converting the coprimate to form a granulate and

iv) compressing the granulate to form the solid oral dosage form.

The process is carried out in the absence of water, i.e. it is a dry compression method. The process may be carried out under ambient conditions of temperature and humidity; it is not necessary to ensure that the process is carried out in a dry atmosphere.

The initial grinding step i) may be carried out according to conventional milling methods or micronisation methods.

The active agent and the additives can be milled either individually or together to particle sizes from about 0.1 μ to about 200 μ, preferably 1.0 μ to 100 μ. At least 90 % of the crystals of both the active agent and the additives are present in these ranges. Particles of this size are obtained by conventional comminution methods, e.g. grinding in an air jet mill, hammer and screen mill, fine impact mill, ball mill or vibrator mill.

Micronisation is preferably effected by known methods using an ultrasonic disintegrator, e.g. of the BRANSON Sonifier type, or by stirring a suspension with a high speed agitator, for example with a stirrer of the HOMOREX type.

The ground particles may optionally at this stage be sieved and mixed according to known methods.

Compression to form a coprimate requires the compaction of the dry ground components. Compaction may be carried out using a slugging technique or preferably, roller compaction. Roller compaction apparatus is conventional and essentially utilises two rollers which roll towards each other. A hydraulic ram forces one of the rollers against the other to exert a compacting force against the ground particles fed into the roller compactor via a screw conveyor system.

A compaction force of between 25 and 65 kN is preferably used. Within this range of compaction forces it has surprisingly been found that for each particular formulation a minimum compaction force should be used in order to obtain a solid oral dosage form wherein the granulate disintegrates into discrete primary particles at a desirable rate, e.g. disintegration occurs approximately six times faster for a solid oral dosage form compressed above a minimum compaction force. Such a rapind disintegration rate is unusual for tablets and is similar to the disintegration rate of a capsule formulation. The particular minimum compaction force is dependent on the active agent content in any given formulation and therefore also depends on the amount and nature of the additives present.

A solid oral dosage form containing an active agent consisting of 80 mg valsartan and 12.5 mg HCTZ, and appropriate additives in appropriate quantities is preferably made by a process wherein the compaction force used to produce the coprimate is at least 30 kN. Appropriate additives in appropriate quantities for this active agent may be 31.5 mg microcrystalline cellulose, 1.5 mg anhydrous colloidal silica, 4.5 mg magnesium stearate and 20 mg crosslinked PVP.

A solid oral dosage form comprising a unit dose of 160 mg valsartan and 12.5 mg HCTZ, and appropriate additives in appropriate quantities is preferably made by a process wherein the compaction force used to produce the coprimate is at least 25 kN. Appropriate additives in appropriate quantities for this active agent may be 75.5 mg microcrystalline cellulose, 3.0 mg anhydrous colloidal silica, 9.0 mg magnesium stearate and 40 mg crosslinked PVP.

Given this information, the skilled addressee would clearly be able to determine the minimum compaction force for other formulations using routine experimentation and without undue burden.

The roller speed is set at between 1 and 15 rpm and is preferably 1.3 to 7.5 rpm. After passing through the rollers the compacted mass (the coprimate) resembles a thin ribbon in segments.

The coprimate may be screened and or milled to produce the granulate. Screening in its simplest form involves the passing of the coprimate emerging from the rollers through a seive under mechanical pressure. More preferably, the coprimate is screened using an oscillating mill, e.g. a MGI 624 Frewitt (Key International Inc.).

The granulate thus formed has a rather wide particle size distribution e.g. from 9 to 340 microns. At this stage of the roller compaction process it is conventional to sort the under-sized and over-sized particles and remove them from the granulate for recycling or recirculation. Thus removed the over- and under-sized particles are typically compacted an additional one or more times in order to obtain the desired particle size distribution of the granulate. Such a process is time consuming and therefore increases the cost of manufacture of solid oral dosage forms. Furthermore, the additional passes through the roller compactor under such high compaction forces can have deleterious effects on the active agent and also render the granulate less suitable for compression into the solid oral dosage form.

It has been found however, that the granulate first emerging from the roller compactor after screening or milling and containing both over- and under-sized particles can in fact be compressed to form solid oral dosage forms without affecting the properties of the solid oral dosage form.

The compression of the granulates to tablet cores can be carried out in a conventional tabletting machine, e.g. in an EK-0 Korsch eccentric tabletting machine or a rotary compression machine, preferably at a compression greater than 2 kN. The tablet cores may vary in shape and be, for example, round, oval, oblong, cylindrical or any other suitable shape, and may also vary in size depending on the concentration of the therapeutic agents. A characteristic of tablets according to the invention is their small size having regard to the amount of active agent contained therein.

In a preferred embodiment of the invention tablets obtained by the compression method described above are slightly oval. The edges of the tablets may be bevelled or rounded.

In a particularly preferred embodiment of the invention a solid oral dosage form is compressed in the form of a tablet having an oblong shape in which the ratio of dimensions length:width:height is 2.5 - 5.0: 0.9 - 2.0: 1.0 and preferably in which the base and top face of the tablet independently of one another are planar or convexly curved about the longitudinal axis; the side faces are planar, the end faces can be of any shape and the edges are optionally bevelled or rounded.

In a particularly preferred embodiment of the invention a solid oral dosage form is compressed, from the granulate, in the form of a tablet of oblong shape in which the length is approximately 10.0 to 11.0 mm, the width approximately 5.0 to 6.0 mm and the height approximately 3.0 to 4.0 mm.

In another particularly preferred embodiment of the invention a solid oral dosage form is compressed from granulates in the form of a tablet of oblong shape in which the length is approximately 15.0 to 16.0 mm, the width approximately 6.0 to 7.0 mm and the height approximately 3.5 to 5.0 mm.

In yet another preferred embodiment of the invention there is provided a tablet which is essentially disc-shaped with the upper and lower faces having a slightly convex surface. Preferably the tablet has a diameter of about 8 to 8.5 mm and a depth of about

3 to 3.5 mm, or a diameter of about 16 mm and a depth of about 6 mm. The tablets may occupy a volume from about 0.1 cm^3 to about 0.45cm^3, more particularly 0.2 to 0.3 cm^3, e.g about 0.125 cm^3 or 0.25 cm^3.

They may furthermore be transparent, colourless or coloured and also marked so as to impart to this product an individual appearance and to make them instantly recognizable. The use of dyes can serve to enhance the appearance as well as to identify the compositions. Dyes suitable for use in pharmacy typically include carotinoids, iron oxides or chlorophyll.

There now follows a series of examples which serve to illustrate the invention.

Example 1

Formula

valsartan	80.0 mg(53.3 %)
hydrochlorothiazide	12.5 mg(8.3 %)
colloidal anhydrous silica AEROSIL	1.5 mg(1.0 %)
microcrystalline cellulose AVICEL	31.5 mg(21.0 %)
polyvinylpyrrolidone CROSPOVIDONE	20.0 mg(13.3 %)
magnesium stearate	4.5 mg(3.0 %)
	150.0 mg

Method

The components except for a portion of the magnesium stearate are blended in a container mixer. The blended material is sieved and pre-blended for an additional period of time in a container mixer.The blended material is compacted using a roller compactor (Bepex Pharmapaktor L 200/50 P, Hosokawa Micron Group) by applying a compaction force of 25-65 kN and a roller speed of 1.3-7.5 rpm. The compacted material is sieved again and the remaining portion of the magnesium stearate is added and final blended in a container mixer. Then 150 mg of the homogenous mixture is compressed into tablets using ovaloid punches (10 x 5.2 mm). The tablets obtained have a length of 10.0-10.2 mm, a width of 5.2-5.4 mm and a height of 3.3-3.9 mm.

Example 1a

A solid oral dosage form prepared according to Example 1 is coated with a film coating formulation:

Cellulose H-P-M683	2.76 mg
Fe Oxide (Yellow) 17268	0.025
Fe Oxide (Red) 17266	0.025
PEG 8000 (flakes)	0.5
Talc PH	2.0
Titanium dioxide PH	0.7
Deionised water	2.5

Ethanol + 5% Isopropyl alcohol	20.0

Method

The PEG and cellulose are dissolved in the deionised water. The remaining components are suspended in the resulting solution. A spray coater apparatus (Dria-coater DRC-500, Powrex Ltd) is charged with the solid oral dosage form of Example 1. The coating formulation is sprayed into the solid oral dosage form rotating in the apparatus at 6-12 rpm. Spray pressure is 1.9 - 2.2 Kg/cm^2 and the spray rate is 5.9 - 7.9 g/min.

Thereafter the coated solid oral dosage form is dried in the coater apparatus at a temperature of 40°C until a moisture content in the coated solid oral dosage form is less than 2.5% by weight.

The tablets obtained have a length of 10.1-10.3 mm, a width of 5.3-5.5 mm and a height of 3.4-4.0 mm

Example 2

Formula

valsartan	160.0 mg(53.3 %)
hydrochlorothiazide	12.5 mg(8.3 %)
colloidal anhydrous silica AEROSIL	3.0 mg(1.0 %)
microcrystalline cellulose AVICEL	75.5 mg(21.0 %)
polyvinylpyrrolidone CROSPOVIDONE	40.0 mg(13.3 %)
magnesium stearate (FAC I)	9.0 mg(3.0 %)
	300.0 mg

A 300.0 mg tablet is formed according to the method described in Example 1. The tablets obtained have a length of 15.0-15.2 mm, a width of 6.0-6.2 mm and a height of 3.9-4.7 mm.

Example 2a

A solid oral dosage form according to Example 2 is coated with a composition (see formulation below) according to the methodology of Example 1a.

Formulation

Cellulose H-P-M683	5.51	mg
Fe Oxide (Red) 17266	0.75	
PEG 8000 (flakes)	1.0	
Talc PH	3.99	
Titanium dioxide PH	0.75	
Deionised water	5.0	
Ethanol + 5% Isopropyl alcohol	40.0	

The tablets obtained have a length of 15.1-15.3 mm, a width of 6.1-6.3 mm and a height of 4.0-4.8 mm.

Example 3

Formula

valsartan	80.0 mg (40%)
AEROSIL 200	10.0 mg (5%)
L-HPC* L-11	87.0 mg (43%)
Magnesium Stearate	3.0 mg (1.5%)

AVICEL PH-301	10.0 mg (5%)
L-HPC* L-21	5.0 mg (2.5%)
AEROSIL 200	1.0 mg (0.5%)
Talc	2.0 mg (1.0%)
Magnesium Stearate	2.0 mg (1.0%)

	200.0 mg

* hydroxypropyl cellulose

Method

The components (above the line) are blended in a container mixer. The blended material is sieved and pre-blended for an additional period of time in a container mixer.The blended material is compacted using a roller compactor (Bepex Pharmapaktor L 200/50 P, Hosokawa Micron Group) by applying a compaction force of 25-65 kN and a roller speed of 1.3-7.5 rpm. The compacted material is sieved again and the components below the line are added and final blended in a container mixer. Then 200 mg of the homogenous mixture is compressed into tablets using ovaloid punches (10 x 5.2 mm). The tablets obtained have a diameter of 8.5 mm and a thickness of 3.9 mm.

Example 3A

Film Coating

Titanium dioxide	1.00 mg
TC-5R*	3.68 mg
PEG 6000	0.66 mg
Talc	2.66 mg
	8.00 mg

* = hydroxypropylmethyl cellulose.

Method

The film coating is applied to the solid oral dosage form of Example 3 according to the methodology of Example 1A.

The coated tablet has a diameter of 8.6 mm and a thickness of 4.0 mm.

21489-9489

CLAIMS:

1. A compressed solid dosage form comprising

a) valsartan or a pharmaceutically acceptable salt thereof; and,

b) at least one pharmaceutically acceptable additive

wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 35% by weight based on the total weight of the compressed solid dosage form.

2. A compressed solid oral dosage form according to claim 1 wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 50% by weight.

3. A compressed solid dosage form according to claim 1 wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount ranging from 57 to 62% by weight.

4. A compressed solid dosage form according to any one of claims 1 to 3, wherein the valsartan or the pharmaceutically acceptable salt thereof is present in a dosage of from between about 10 and 250 mg.

5. A compressed solid dosage form according to claim 4, wherein the dosage range is from 40 to 160 mg.

6. A compressed solid dosage form according to claim 4, wherein the dosage is 40 mg, 80 mg or 160 mg.

7. A compressed solid dosage form according to any one of claims 1 to 3 further comprising hydrochlorothiazide (HCTZ).

8. A compressed solid dosage form which comprises valsartan or a pharmaceutically acceptable salt thereof; HCTZ; and,

at least one pharmaceutically acceptable additive; wherein the valsartan or the pharmaceutically acceptable salt thereof and the HCTZ are present in an amount of more than 35% by weight based on the total weight of the compressed solid dosage form.

9. A compressed solid dosage form according to claim 8 comprising a unit dose of about 10 to 250 mg of the valsartan or the pharmaceutically acceptable salt thereof and a unit dose of about 6 to 60 mg of the HCTZ.

10. A compressed solid dosage form according to claim 8 comprising a unit dose of about 50 to 100 mg of the valsartan or the pharmaceutically acceptable salt thereof and a unit dose of about 10 to 30 mg of the HCTZ.

11. A compressed solid dosage form according to claim 8 comprising a unit dose of about 80 to 160 mg of the valsartan or the pharmaceutically acceptable salt thereof and a unit dose of about 12.5 mg or 25 mg of the HCTZ.

12. A compressed solid dosage form according to any one of claims 1 to 11, wherein the at least one pharmaceutically acceptable additive comprises microcrystalline cellulose.

13. A compressed solid dosage form according to claim 12, wherein the microcrystalline cellulose is present in an amount of from 15 to 25% by weight.

14. A compressed solid dosage form according to any one of claims 1 to 13, wherein the at least one pharmaceutically acceptable additive comprises crosslinked polyvinylpyrrolidone (PVP).

15. A compressed solid dosage form according to claim 14, wherein the crosslinked PVP is present in an amount of from 10 to 30% by weight.

16. A compressed solid dosage form according to any one of claims 1 to 15 in the form of a tablet.

17. A compressed solid dosage form according to any one of claims 1 to 15 in the form of a dragee.

18. A process of forming a compressed solid dosage form comprising more than 35% by weight of valsartan or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable additive wherein the process comprises the steps of:

i) blending the valsartan or the salt thereof and the at least one pharmaceutically acceptable additive to form a mixture;

ii) subjecting the mixture to compression to form a coprimate;

iii) converting the coprimate into a granulate; and,

iv) compressing the granulate to form the compressed solid dosage form.

19. The process according to claim 18, wherein the blending step includes grinding.

20. A process according to claim 18 or 19 wherein the compression step ii) is carried out using roller compaction or slugging techniques.

21. A process according to claim 18 or 19, wherein the coprimate is formed by compression in the absence of water.

22. A process according to any one of claims 18 to 21, wherein step iii) is carried out by screening or milling the coprimate.

23. A process according to any one of claims 18 to 22 wherein the granulate is compressed without first being sized.

24. A process according to any one of claims 18 to 23 wherein the granulate is formed under a pressure of from about 25 to about 65 kN.

25. A coprimate obtained as an intermediate by roller compaction or slugging in the process defined in claim 20.

26. A granulate obtained as an intermediate in the process defined in any one of claims 18 to 22.

27. A compressed solid dosage form produced according to the process as defined in any one of claims 18 to 24.

28. A compressed solid dosage form according to any one of claims 1 to 17 for treating hypertension, congestive heart failure, angina, myocardial infarction, arteriosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, stroke, left ventricular hypertrophy, cognitive dysfunction, headache, or chronic heart failure.

29. A process of forming a compressed solid dosage form comprising more than 35% by weight of valsartan or a

pharmaceutically acceptable salt thereof, HCTZ and at least one pharmaceutically acceptable additive wherein the process comprises the steps of:

i) blending the valsartan, or the salt thereof, the HCTZ and the at least one pharmaceutically acceptable additive to form a mixture;

ii) subjecting the mixture to compression to form a coprimate;

iii) converting the coprimate into a granulate; and,

iv) compressing the granulate to form the compressed solid dosage form.

30. The process according to claim 29 wherein the blending step includes grinding.

31. A process according to claim 29 or 30 wherein the compression step ii) is carried out using roller compaction or slugging techniques.

32. A process according to claim 29 or 30 wherein the coprimate is formed by compression in the absence of water.

33. A process according to claim 29 or 30 wherein step iii) is carried out by screening or milling the coprimate.

34. A process according to any one of claims 29 to 33 wherein the granulate is compressed without first being sized.

35. A process according to any one of claims 29 to 34 wherein the granulate is formed under a pressure of from about 25 to about 65 kN.

36. A coprimate obtained as an intermediate for forming a compressed solid dosage form comprising more than 35% by weight of valsartan or a pharmaceutically acceptable salt thereof, HCTZ and at least one pharmaceutically acceptable additive in a process comprising the steps of:

i) blending the valsartan, or the salt thereof, the HCTZ and the at least one pharmaceutically acceptable additive to form a mixture;

ii) subjecting the mixture to compression by means of roller compaction or slugging to form the coprimate.

37. A granulate obtained as an intermediate for forming a compressed solid dosage form comprising more than 35% by weight of valsartan or a pharmaceutically acceptable salt thereof, HCTZ and at least one pharmaceutically acceptable additive in a process comprising:

i) blending the valsartan, or the salt thereof, the HCTZ and the at least one pharmaceutically acceptable additive to form a mixture;

ii) subjecting the mixture to compression to form a coprimate;

iii) converting the coprimate into the granulate.

38. A granulate according to claim 37, wherein the blending step includes grinding.

39. A granulate according to claim 37 or 38, wherein the compression step is carried out using roller compaction or slugging techniques.

40. A granulate according to claim 37 or 38, wherein the coprimate is formed by compression in the absence of water.

41. A granulate according to claim 37 or 38, wherein the coprimate is converted to the granulate by screening or milling the coprimate.

42. A compressed solid dosage form produced according to the process as defined in any one of claims 29 to 35.

43. A compressed solid dosage form according to any one of claims 1 to 17, wherein the dimension ratio of the dosage forms length:width:height is 2.5-5.0:0.9-2.0:1.0.

44. A compressed solid dosage form according to any one of claims 1 to 17 wherein the dosage form has a length of approximately 10 to 11 mm, a width of approximately 5.0-6.0 mm and a height of approximately 3.0-4.0 mm.

45. A compressed solid dosage form according to any one of claims 1 to 17 wherein the dosage form has a length of approximately 15.0-16.0 mm, a width of approximately 6.0-7.0 mm and a height of approximately 3.5 to 5.0 mm.

46. A compressed solid dosage form according to any one of claims 1 to 17 wherein the dosage form has a diameter of about 8 to 8.5 mm and a depth of about 3 to 3.5 mm.

47. A compressed solid dosage form according to any one of claims 1 to 17 wherein the dosage form has a diameter of about 16 mm and a depth of about 6 mm.

48. A compressed solid dosage form according to any one of claims 1 to 17 for oral administration.

49. A dry-compressed solid oral dosage form comprising

(a) valsartan or a pharmaceutically acceptable salt thereof and

(b) at least one pharmaceutically acceptable additive; wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 35 % by weight based on the total weight of the compressed solid oral dosage form.

50. A dry-compressed solid oral dosage form according to claim 49, wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of 40 % to 65 % by weight.

51. A dry-compressed solid oral dosage form according to claim 49, wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of 45 % to 65 % by weight.

52. A dry-compressed solid oral dosage form according to claim 49, wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 50 % by weight.

53. A dry-compressed solid oral dosage form according to claim 49, wherein the valsartan or the pharmaceutically acceptable salt thereof is present in a unit dose of 40 mg to 160 mg.

54. A dry-compressed solid oral dosage form according to claim 49, further comprising hydrochlorothiazide (HCTZ).

55. A dry-compressed solid oral dosage form according to claim 54, wherein the valsartan or the pharmaceutically acceptable salt thereof is present in a dose range from 10 to 250 mg and the HCTZ in a dose range from 6 to 60 mg.

56. A dry-compressed solid oral dosage form according to claim 54, wherein the valsartan or the pharmaceutically

acceptable salt thereof is present in a unit dose of 80 or 160 mg and the HCTZ in a unit dose of 12.5 mg or 25 mg.

57. A dry-compressed solid oral dosage form according to claim 54, wherein (i) the valsartan or the pharmaceutically acceptable salt thereof is present in a unit dose of 80 mg and the HCTZ in a unit dose of 12.5 mg or 25 mg or (ii) the valsartan is present in a unit dose of 160 mg and the HCTZ in a unit dose of 12.5 mg or 25 mg.

58. A dry-compressed solid oral dosage form according to any one of claims 49 to 57, wherein the additive comprises a disintegrant.

59. A dry-compressed solid oral dosage form according to claim 58, wherein the disintegrant is present in an amount of 2 to 20 % by weight.

60. A dry-compressed solid oral dosage form according to claim 58, wherein the disintegrant is present in an amount of 15% by weight.

61. A dry-compressed solid oral dosage form according to any one of claims 58 to 60, wherein the disintegrant is selected from the group consisting of CMC-Ca, CMC-Na, crosslinked PVP, alginic acid, crospovidone sodium alginate, guar, and CMC.

62. A dry-compressed solid oral dosage form according to any one of claims 58 to 60, wherein the disintegrant is crospovidone.

63. A dry-compressed solid oral dosage form according to any one of claims 58 to 60, wherein the disintegrant is crosslinked PVP.

64. A dry-compressed solid oral dosage form according to claim 63, wherein the crosslinked PVP is present in a range of 10 to 20 % by weight.

65. A dry-compressed solid oral dosage form according to any one of claims 49 to 64, wherein the additive comprises a binder.

66. A dry-compressed solid oral dosage form according to claim 65, wherein the binder is selected from the group consisting of a starch, microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose and hydroxypropylmethyl cellulose.

67. A dry-compressed solid oral dosage form according to claim 65, wherein the binder is selected from the group consisting of potato starch, wheat starch and corn starch.

68. A dry-compressed solid oral dosage form according to any one of claims 65 to 67, wherein the binder is present in a range of 10 % to 45 % by weight.

69. A dry-compressed solid oral dosage form according to any one of claims 65 to 67, wherein the binder is present in a range of 20 to 30 % by weight.

70. A dry-compressed solid oral dosage form according to claim 65, wherein the binder is microcrystalline cellulose.

71. A dry-compressed solid oral dosage form according to claim 70, wherein microcrystalline cellulose is present in an amount of 10 to 30 % by weight.

72. A dry-compressed solid oral dosage form according to any one of claims 49 to 71, wherein the additive comprises a glidant.

73. A dry-compressed solid oral dosage form according to claim 72, wherein the glidant is selected from the group consisting of colloidal silica, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

74. A dry-compressed solid oral dosage form according to claim 72, wherein the glidant is colloidal silica.

75. A dry-compressed solid oral dosage form according to any one of claims 72 to 74, wherein the glidant is present in an amount of 0.1 to 5 % by weight.

76. A dry-compressed solid oral dosage form according to any one of claims 49 to 71, wherein the additive comprises a lubricant.

77. A dry-compressed solid oral dosage form according to claim 76, wherein the lubricant is selected from the group consisting of Mg, Al, Ca stearate, PEG 4000-8000 and talc.

78. A dry-compressed solid oral dosage form according to claim 76, wherein the lubricant is Mg stearate.

79. A dry-compressed solid oral dosage form according to claim 78, wherein Mg stearate is present in an amount of 0.1 % to 5 % by weight.

80. A dry-compressed solid oral dosage form according to any one of claims 49 to 79, wherein the additive comprises a filler or diluent.

81. A dry-compressed solid oral dosage form according to 80, wherein the filler or diluent is selected from the group consisting of confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, lactose, mannitol,

microcellulose, powdered cellulose, sorbitol, sucrose and talc.

82. A dry-compressed solid oral dosage form according to claim 80, wherein the filler or diluent is microcrystalline cellulose.

83. A dry-compressed solid oral dosage form according to any one of claims 80 to 82, wherein the filler or diluent is present in a range from 15 to 40 % by weight.

84. A dry-compressed solid oral dosage form according to claim 54, wherein the dosage form comprises:

valsartan	80.0 mg (53.3%)
hydrochlorothiazide	12.5 mg (8.3%)
colloidal anhydrous silica	1.5 mg (1.0%)
microcrystalline cellulose	31.5 mg (21.0%)
polyvinylpyrrolidone	20.0 mg (13.3%)
magnesium stearate	4.5 mg (3.0%)

85. A dry-compressed solid oral dosage form according to claim 54, wherein the dosage form comprises:

valsartan	160.0 mg (53.3%)
hydrochlorothiazide	12.5 mg (8.3%)
colloidal anhydrous silica	3.0 mg (1.0%)
microcrystalline cellulose	75.5 mg (21.0%)
polyvinylpyrrolidone	40.0 mg (13.3%)
magnesium stearate	9.0 mg (3.0%)

86. A dry-compressed solid oral dosage form according to claim 49, wherein the dosage form comprises:

valsartan	80.0 mg (40%)
colloidal silica 200	10.0 mg (5%)
L-HPC* L-11	87.0 mg (43%)
Magnesium Stearate	3.0 mg (1.5%)
microcrystalline cellulose 301	10.0 mg (5%)
L-HPC* L-21	5.0 mg (2.5%)
colloidal silica 200	1.0 mg (0.5%)
Talc	2.0 mg (1.0%)
Magnesium stearate	2.0 mg (1.0%)

* hydroxypropyl cellulose

87. A dry-compressed solid oral dosage form according to any one of claims 49 to 86, for use in treatment of a disease selected from hypertension, congestive heart failure, angina, myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, Alzheimer's disease, stroke, headache, and chronic heart failure.

88. A dry-compressed solid oral dosage form according to claim 87, wherein the hypertension is selected from the group consisting of malignant hypertension, essential hypertension, renovascular hypertension, diabetic hypertension, isolated systolic and other secondary hypertension.

89. A dry-compressed solid oral dosage form according to claim 87, wherein the disease is stable angina.

90. A dry-compressed solid oral dosage form according to claim 87, wherein the disease is unstable angina.

91. A process of making a solid oral dosage form comprising

a) valsartan or a pharmaceutically acceptable salt thereof and

b) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods; wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 35% by weight based on the total weight of the compressed solid oral dosage form;

wherein the process comprises the steps of:

i) grinding the active agent and pharmaceutically acceptable additives,

ii) subjecting a mixture of the ground active agent and additives to compression to form a comprimate, wherein compression to form a comprimate requires the compaction of the dry ground components,

iii) converting the comprimate into granulate and

iv) compressing the granulate to form the solid oral dosage form.

92. A solid dosage form according to any one of claims 1 to 17, 27, 28, and 42 to 90 exhibiting accelerated release.

93. A solid oral dosage form according to claim 92, exhibiting 90 % release within a ten minute period.

94. A solid oral dosage form according to claim 92, exhibiting 90 % release within a five minute period.

95. A compressed tablet comprising

a) 80 mg valsartan or a pharmaceutically acceptable salt thereof and

b) pharmaceutically acceptable additives suitable for the preparation of compressed tablets; wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 35% by weight based on total weight of the compressed tablet.

96. A compressed tablet according to claim 95, further comprising 12.5 mg of hydrochlorothiazide (HCTZ).

97. A compressed tablet according to claim 95, comprising 31.5 mg microcrystalline cellulose as one of the additives.

98. A compressed tablet according to claim 96 or 97, comprising 20 mg crosslinked PVP as one of the additives.

99. A compressed tablet according to any one of claims 96 to 98 comprising 4.5 mg magnesium stearate as one of the additives.

100. A compressed tablet according to any one of claims 96 to 99 comprising 1.5 mg anhydrous colloidal silica as one of the additives.

101. A compressed tablet according to claim 95, further comprising 25 mg of hydrochlorothiazide (HCTZ).

102. A compressed tablet according to any one of claims 95, 96 and 101, which comprises microcrystalline cellulose as one of the pharmaceutically acceptable additives.

103. A compressed tablet according to claim 102, wherein the microcrystalline cellulose is present in an amount of from 15 to 40 % by weight.

104. A compressed tablet according to claim 102, wherein the microcrystalline cellulose is present in an amount of from 15 to 25 % by weight.

105. A compressed tablet according to any one of claims 95, 96, 101 and 102 to 104, which comprises crosslinked polyvinylpyrrolidone (PVP) as one of the pharmaceutically acceptable additives.

106. A compressed tablet according to claim 105, wherein the crosslinked PVP is present in an amount of from 2 to 20 % by weight.

107. A compressed tablet according to any one of claims 95 to 106, exhibiting accelerated release.

108. A compressed tablet according to claim 107, exhibiting 90 % release within a ten minute period.

109. A compressed tablet according to claim 107, exhibiting 90 % release within a five minute period.

110. A compressed tablet according to any one of claims 95 to 106, exhibiting delayed release.

111. A compressed tablet according to any one of claims 95 to 110, having an oblong shape in which the ratio of dimensions length : width : height is 2.5 - 5.0 : 0.9 - 2.0 : 1.0.

112. A compressed tablet according to any one of claims 95 to 110, having an oblong shape in which the length is 10.0 to 11.0 mm, the width 5.0 to 6.0 mm and the height 3.0 to 4.0 mm or an oblong shape in which the length is 15.0 to 16.0 mm, the width 6.0 to 7.0 mm and the height 3.5 to 4.5 mm.

113. A compressed tablet according to any one of claims 95 to 112 having a volume from about 0.1 cm^3 to 0.45 cm^3.

114. A compressed tablet according to any one of claims 95 to 112 having a volume from about 0.2 cm^3 to 0.3 cm^3.

115. A solid oral dosage form comprising

a) 160 mg valsartan or a pharmaceutically acceptable salt thereof and

b) pharmaceutically acceptable additives suitable for the preparation of solid oral dosage forms by compression methods; wherein the valsartan or the pharmaceutically acceptable salt thereof is present in an amount of more than 35% by weight based on total weight of the solid oral dosage form.

116. A solid oral dosage form according to claim 115, further comprising 12.5 mg of hydrochlorothiazide (HCTZ).

117. A solid oral dosage form according to claim 115 comprising 75.5 mg microcrystalline cellulose as one of the additives.

118. A solid oral dosage form according to claim 116 or 117 comprising 40 mg crosslinked PVP as one of the additives.

119. A solid oral dosage form according to any one of claims 116 to 118 comprising 9.0 mg magnesium stearate as one of the additives.

120. A solid oral dosage form according to any one of claims 117 to 119 comprising 3.0 mg anhydrous colloidal silica as one of the additives.

121. A solid oral dosage form according to claim 116, further comprising 25 mg of hydrochlorothiazide (HCTZ).

122. A solid oral dosage form according to any one of claims 115, 116, and 121, which comprises microcrystalline cellulose as one of the pharmaceutically acceptable additives.

21489-9489

123. A solid oral dosage form according to claim 122, wherein the microcrystalline cellulose is present in an amount of from 15 to 40 % by weight.

124. A solid oral dosage form according to claim 122, wherein the microcrystalline cellulose is present in an amount of from 15 to 25 % by weight.

125. A solid oral dosage form according to any one of claims 115, 116, and 121 to 124, which comprises crosslinked polyvinylpyrrolidone (PVP) as one of the pharmaceutically acceptable additives.

126. A solid oral dosage form according to claim 125, wherein the crosslinked PVP is present in an amount of from 2 to 20 % by weight.

FETHERSTONHAUGH & CO.

OTTAWA, CANADA

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