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(54) Title: DISPERSIBLE TABLET FOR ORAL ADMINISTRATION

(57) Abstract: The present invention is directed to pharmaceutical compositions or dispersible tablets for oral administration comprising N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide (macitentan), the use of said pharmaceutical compositions or dispersible tablets for the treatment of pulmonary hypertension and the process for preparing such dispersible tablets.

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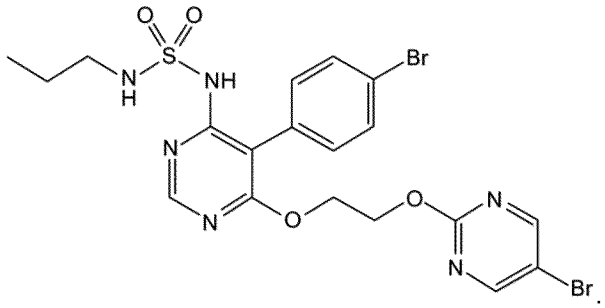
DISPERSIBLE TABLET FOR ORAL ADMINISTRATION

FIELD OF THE INVENTION

The present invention is directed to novel pharmaceutical compositions (e.g. dispersible tablets for oral administration) comprising *N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-*N'*-propylsulfamide (also known as macitentan), the use of said pharmaceutical compositions for the treatment of pulmonary hypertension (preferably pulmonary arterial hypertension) or of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients (especially in Fontan-palliated patients), and processes for preparing said pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Macitentan is an endothelin receptor inhibitor, useful as an endothelin receptor antagonist. Macitentan and the preparation thereof are described in WO 02/053557. Macitentan has the following structure:



Macitentan is an endothelin receptor antagonist that acts as an antagonist of two endothelin (ET) receptor subtypes, ETA and ETB (Kholdani et al, Macitentan for the treatment of pulmonary arterial hypertension. Vasc. Health

Risk Manag. (2014), 10, 665-673). Currently, macitentan is taken as a 10 mg oral dose once a day in adult pulmonary arterial hypertension patients.

Previous formulations of macitentan pediatric dispersible tablets have been studied and shown to be biocomparable to adult film-coated tablet formulations and well tolerated (Sidharta et al., Pharmacol. Res. Perspect., 2020, 1-8). These pediatric macitentan dispersible tablets have an inner phase containing 0.5, 2.5 or 5 mg of macitentan, delta-mannitol, croscarmellose sodium and isomalt, and an outer phase comprising mannitol, croscarmellose sodium, isomalt and magnesium stearate (Table 1) and were prepared according to a process summarized by the flow chart shown in Figure 1 (wet granulation).

Table 1 *Composition of the 0.5 mg, 2.5 mg and 5.0 mg bi-phasic Macitentan oral dispersible tablets prepared by wet granulation.*

		Quantity per Unit (mg)		
Component	Function	0.5 mg tablets	2.5 mg tablets	5.0 mg tablets
Intragranular Phase				
Macitentan	Active Ingredient	0.5	2.5	5.0
Delta-Mannitol	Filler	29.5	27.5	25.0
Isomalt	Binder	2.5	2.5	2.5
Sodium Croscarmellose	Disintegrant	2.5	2.5	2.5
Purified Water [a]	Solvent	q.s.	q.s.	q.s.
Extragranular Phase				
Parteck ® ODT	Filler/Disintegrant	9.5	9.5	9.5
Isomalt	Binder/compressibility enhancer	2.5	2.5	2.5
Sodium Croscarmellose	Disintegrant	2.5	2.5	2.5
Magnesium Stearate	Lubricant	0.5	0.5	0.5
Tablet		50.0	50.0	50.0

[a] Removed during processing

[b] Parteck ® ODT (orally disintegrating tablet) is a combination of specifically spray-granulated mannitol and croscarmellose sodium.

The development of tablets of potent drugs poses several challenges, including the insurance of a homogenous distribution of active pharmaceutical ingredient (API) is of concern due to inadequate uniformity could result in failure of therapy. The difficulty of distributing a small amount of API evenly

into a large mass of excipients is a commonly recognized technical challenge. For this reason, typically low dose solids are often manufactured through a wet granulation process (Table 1, Figure 1).

Technical challenges with respect to compressibility and type of excipients may however arise, limiting the robustness of the wet granulation process. Thus, in the specific case of macitentan, there was the need to design particular pharmaceutical compositions or dispersible tablets comprising macitentan fulfilling special technical requirements and overcoming the previously mentioned technical challenges. To overcome these challenges, direct compression (DC) process was explored to optimize the manufacturing process and the specific compositions conceived for that purpose surprisingly exhibited improved uniformity for homogenous distribution of API.

Direct Compression (DC) is the most straightforward manufacturing option, with the fewest manufacturing steps, making it the easiest to control and least expensive. The DC tablet manufacturing process uses two primary process steps: blending the API with excipients and compressing the finished tablets. Because of the simplicity of the process, the DC process is directly impacted by material properties. DC requires increased performance, quality, and consistency from starting ingredients, including excipients. As δ-mannitol is specifically designed for wet granulation, conversion to a DC process implicates the need for change to a β-mannitol. The main drawback of the commonly used β polymorph of mannitol in tablet formulations is its low compressibility.

SUMMARY OF THE INVENTION

The present invention is directed to pharmaceutical compositions (e.g. dispersible compositions) comprising macitentan or a pharmaceutically acceptable salt, solvate, hydrate or morphological form thereof; methods of preparation of said pharmaceutical compositions; and method of treating pulmonary hypertension (preferably pulmonary arterial hypertension), or of treating pulmonary vascular disease and/or cardiac dysfunction in functional

single ventricular heart disease patients (especially in Fontan-palliated patients), comprising administration of said pharmaceutical compositions.

Within the context of this disclosure, any reference to macitentan is to be understood as referring also to the pharmaceutically acceptable salts or solvates, including hydrates as well as to the morphological forms thereof, if not indicated otherwise and where appropriate and expedient.

In certain embodiments, the present invention is directed to a pharmaceutical composition comprising macitentan, and β-mannitol; wherein said pharmaceutical composition exhibits improved AP content uniformity, homogenous distribution of API with improved process for ease of making , particularly at commercial scale.

An embodiment of the present invention is directed to a pharmaceutical composition or dispersible tablet comprising:

a. macitentan,
b. β-mannitol,
c. isomalt
d. croscarmellose sodium, and
e. magnesium stearate.

In another embodiment of the present invention is directed to a pharmaceutical composition or dispersible tablet comprising:

a. about 0.5-20% w/w macitentan,
b. about 0.1-90% w/w mannitol,
c. about 0.1-90% w/w of isomalt,
d. about 5-20% w/w of croscarmellose sodium, and
e. about 0.5-5% w/w of magnesium stearate.

In another embodiment of the present invention is directed to a pharmaceutical composition or dispersible tablet comprising:

a. about 0.5-5% w/w macitentan,

b. about 0.1-90% w/w mannitol,
c. about 0.1-90% w/w of isomalt,
d. about 5-20% w/w of croscarmellose sodium, and
e. about 0.5-5% w/w of magnesium stearate.

In a further embodiment of the present invention is directed to a pharmaceutical composition or dispersible tablet comprising:

a. about 1% w/w macitentan,
b. about 75% w/w mannitol,
c. about 10% w/w of isomalt,
d. about 11% w/w of croscarmellose sodium, and
e. about 3% w/w of magnesium stearate.

In various embodiments, the present invention is directed to a pharmaceutical composition comprising macitentan. In various embodiments, the pharmaceutical composition comprises macitentan and β-mannitol. In various embodiments, the pharmaceutical composition comprises macitentan, β-mannitol, and one or more of isomalt, croscarmellose sodium, and magnesium stearate.

In an embodiment, the present invention is directed to a dispersible tablet comprising macitentan. In various embodiments, the dispersible tablet comprises macitentan and β-mannitol. In various embodiments, the dispersible tablet includes macitentan, β-mannitol, and one or more of isomalt, croscarmellose sodium, and magnesium stearate.

In another embodiment, the present invention is directed to a method of preparing a pharmaceutical composition comprising macitentan. In various embodiments, the present invention is directed to a method or preparing a pharmaceutical composition comprises macitentan and β-mannitol. In various embodiments, the present invention is directed to a method of preparing a pharmaceutical composition comprising macitentan, β-mannitol, and one or more of isomalt, croscarmellose sodium, and magnesium stearate.

In another embodiment, the present invention is directed to a method for preparing dispersible tablets comprising macitentan. In various embodiments, the present invention is directed to a method for preparing dispersible tablets comprise macitentan and β-mannitol. In various embodiments, the present invention is directed to a method for preparing dispersible tablets comprise macitentan, β-mannitol, isomalt, croscarmellose sodium, and magnesium stearate.

In an embodiment, the instant invention is directed to a method of treating pulmonary arterial hypertension by administering to a patient in need thereof a pharmaceutical composition as described herein.

In an embodiment, the instant invention is directed to a method of treating pulmonary arterial hypertension by administering to a patient in need thereof a pharmaceutical composition comprising macitentan and β-mannitol.

In an embodiment, the instant invention is directed to a method of treating pulmonary arterial hypertension by administering to a patient in need thereof a pharmaceutical composition comprising macitentan, β-mannitol, and one or more of isomalt, croscarmellose sodium, and magnesium stearate. In an embodiment, the instant invention is directed to a method of treating pulmonary arterial hypertension comprising administering to a patient in need thereof a pharmaceutical composition comprising macitentan, β-mannitol, isomalt, croscarmellose sodium, and magnesium stearate.

In an embodiment, the instant invention is directed to a method of treating pulmonary arterial hypertension comprising administering to a patient in need thereof a dispersible tablet as described herein. In an embodiment, the instant invention is directed to a method of treating pulmonary arterial hypertension comprising administering to a patient in need thereof a dispersible tablet comprising macitentan and β-mannitol. In an embodiment, the instant invention is directed to a method of treating pulmonary arterial hypertension comprising administering to a patient in need thereof a dispersible tablet comprising macitentan, β-mannitol, and one or more of isomalt, croscarmellose

sodium, and magnesium stearate. In an embodiment, the instant invention is directed to a method of treating pulmonary arterial hypertension comprising administering to a patient in need thereof a dispersible tablet comprising macitentan, β-mannitol, isomalt, croscarmellose sodium, and magnesium stearate.

In certain embodiments of the instant invention, the pulmonary hypertension is pulmonary arterial hypertension.

In particular, the pulmonary hypertension or pulmonary arterial hypertension patients to whom the previously described methods of treatment are addressed will be pediatric patients, i.e. patients aged 18 years or less.

In another embodiment, the instant invention is directed to a method of treating pulmonary vascular disease and/or cardiac dysfunction in a Functional Single Ventricular Heart Disease (FVSHD) patient comprising administering to said patient in need thereof a pharmaceutical composition as described herein.

In an embodiment, the instant invention is directed to a method of treating pulmonary vascular disease and/or cardiac dysfunction in a FSVHD patient comprising administering to said patient in need thereof a pharmaceutical composition comprising macitentan and β-mannitol.

In an embodiment, the instant invention is directed to a method of treating pulmonary vascular disease and/or cardiac dysfunction in a FSVHD patient comprising administering to said patient in need thereof a pharmaceutical composition comprising macitentan, β-mannitol, and one or more of isomalt, croscarmellose sodium, and magnesium stearate. In an embodiment, the instant invention is directed to a method of treating pulmonary vascular disease and/or cardiac dysfunction in a FSVHD patient comprising administering to said patient in need thereof a pharmaceutical composition comprising macitentan, β-mannitol, isomalt, croscarmellose sodium, and magnesium stearate.

In an embodiment, the instant invention is directed to a method of treating pulmonary vascular disease and/or cardiac dysfunction in a FSVHD patient comprising administering to said patient in need thereof a dispersible tablet as described herein. In an embodiment, the instant invention is directed to a method of treating pulmonary arterial hypertension comprising administering to a patient in need thereof a dispersible tablet comprising macitentan and β-mannitol. In an embodiment, the instant invention is directed to a method of treating pulmonary vascular disease and/or cardiac dysfunction in a FSVHD patient comprising administering to said patient in need thereof a dispersible tablet comprising macitentan, β-mannitol, and one or more of isomalt, croscarmellose sodium, and magnesium stearate. In an embodiment, the instant invention is directed to a method of treating pulmonary vascular disease and/or cardiac dysfunction in a FSVHD patient comprising administering to said patient in need thereof a dispersible tablet comprising macitentan, β-mannitol, isomalt, croscarmellose sodium, and magnesium stearate.

In certain embodiments of the instant invention, the FSVHD patients in whom the pulmonary vascular disease and/or cardiac dysfunction is treated are Fontan-palliated patients.

In particular, the FSVHD patients to whom the previously described methods of treatment are addressed will be pediatric patients, i.e. patients aged 18 years or less.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a flowchart of Batch Manufacturing Process of the 0.5 mg, 2.5 mg and 5.0 mg oral dispersible tablets by wet granulation.

Figure 2 shows a flowchart of Batch Manufacturing Process for the 1 mg and 2.5 mg oral dispersible tablet by direct compression according to the instant invention.

Figure 3 shows the stability profile for the different grades of β-mannitol excipients used in the manufacturing process. This Figure shows the amount of 6-amino-5-(4-bromophenyl)-5-(2-((5-bromopyrimidin-2-yl)oxy)ethoxy)-pyrimidine ("Compound A" - hydrolysis degradation product of macitentan) within the tablet after storage conditions 50 °C / 10% relative humidity (RH) and 50 °C / 75% RH in comparison with the initial profile.

Figure 4(a) shows the compression force – hardness profile comparison of the wet granulation tablets versus the direct compression tablets. A higher tablet hardness is achieved at lower compression forces for the DC formula compression force -hardness profile

Figure 4(b) shows the compression force - disintegration time profile comparison of the wet granulation tablets versus the direct compression tablets.

Figure 4(c) shows the dissolution profile of the wet granulation vs. direct compression formulations.

Figure 5 shows the dissolution profile comparison of macitentan dispersible tablets containing 1 up to 3% magnesium stearate. An increase in magnesium stearate up to 3% did not impact on the dissolution of the macitentan dispersible tablets.

Figure 6 shows the dissolution profiles for three different macitentan dispersible tablet dose strengths: 1 mg, 2.5 mg, and 3.5 mg.

DETAILED DESCRIPTION

The present invention is directed to pharmaceutical compositions or dispersible tablets comprising macitentan or a pharmaceutically acceptable salt, solvate, hydrate or morphological form thereof; methods of preparation of said pharmaceutical compositions; and methods of treating pulmonary hypertension or of treating pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients (especially in Fontan-palliated patients), comprising administration of said pharmaceutical compositions or dispersible tablets.

One skilled in the art will recognize that wherein the term “macitentan” is used in the description of an embodiment of the present invention, it is intended that said term include macitentan as well as pharmaceutically acceptable salts, solvates, hydrates and morphological forms thereof.

The present invention is directed to a pharmaceutical composition comprising macitentan, and β-mannitol. In various embodiments, the present invention is directed to a pharmaceutical composition comprising macitentan, β-mannitol, and one or more of isomalt, croscarmellose sodium, and magnesium stearate.

In various embodiments, the present invention is directed to pharmaceutical compositions wherein macitentan is present in an amount in the range from about 0.5 mg to about 10 mg, or any amount or range thereof; more preferably in an amount in the range of from about 1 mg to about 5 mg, or any amount or range thereof. In various embodiments, the present invention is directed to pharmaceutical compositions wherein macitentan is present in an amount of about 1 mg, about 2.5 mg, about 3.5 mg or about 5.0 mg.

In various embodiments, the present invention is directed to a pharmaceutical composition comprising the amount of macitentan may vary from 0.5-20% w/w, and the amount of β-mannitol may vary from 0.1-90% w/w. In various embodiments, the instant invention is directed to a pharmaceutical composition comprising macitentan in an amount that may vary from 1% w/w, β-mannitol in an amount that may vary from 0.1-90% w/w, and one or more of isomalt in an amount that may vary from 0.1-90% w/w, croscarmellose sodium in an amount that may vary from 5-20% w/w and magnesium stearate in an amount that may vary from 0.5-5% w/w.

In various embodiments, the present invention is directed to a pharmaceutical composition comprising the amount of macitentan may vary from 0.5-5% w/w, and the amount of β-mannitol may vary from 0.1-90% w/w. In various embodiments, the instant invention is directed to a pharmaceutical composition comprising macitentan in an amount that may vary from 0.5-5% w/w, β-mannitol in an amount that may vary from 0.1-90% w/w, and one or

more of isomalt in an amount that may vary from 0.1-90% w/w, croscarmellose sodium in an amount that may vary from 5-20% w/w and magnesium stearate in an amount that may vary from 0.5-5% w/w.

In an embodiment, the present invention is notably directed to a pharmaceutical composition comprising macitentan in an amount of 0.9-1.1% w/w, β-mannitol in an amount of 67.5-82.5% w/w, isomalt in an amount of 9-11% w/w, croscarmellose sodium in an amount of 9.9-12.1% w/w and magnesium stearate is present in an amount of about 2.7-3.3% w/w, for example a pharmaceutical composition comprising macitentan in an amount of 1% w/w, β-mannitol in an amount of 75% w/w, isomalt in an amount of 10% w/w, croscarmellose sodium in an amount of 11% w/w and magnesium stearate is present in an amount of 3% w/w.

In an embodiment, the instant invention is directed to a pharmaceutical composition comprising macitentan in an amount of about 1% w/w, β-mannitol in an amount of about 75% w/w, isomalt in an amount of about 10% w/w, croscarmellose sodium in an amount of about 11% w/w and magnesium stearate is present in an amount of about 3% w/w.

The present invention is directed to a dispersible tablet comprising macitentan, and β-mannitol. In various embodiments, the present invention is directed to a dispersible tablet comprising macitentan, β-mannitol, and one or more of isomalt, croscarmellose sodium, and magnesium stearate.

In various embodiments, the present invention is directed to a dispersible tablet comprising macitentan present in an amount in the range from about 0.5 mg to about 10 mg, or any amount or range thereof; more preferably in an amount in the range of from about 1 mg to about 5 mg, or any amount or range thereof. In various embodiments, the present invention is directed to dispersible tablet wherein macitentan is present in an amount of about 1 mg, about 2.5 mg, about 3.5 mg or about 5.0 mg.

In another embodiment, the present invention is directed to a dispersible tablet comprising macitentan in the amount that may vary from 0.5-20% w/w,

and the amount of β-mannitol may vary from 0.1-90% w/w. In various embodiments, the instant invention is directed to a dispersible tablet comprising macitentan in an amount that may vary from 0.5-20% w/w, β-mannitol in an amount that may vary from 0.1-90% w/w, and one or more of isomalt in an amount that may vary from 0.1-90% w/w, croscarmellose sodium in an amount that may vary from 5-20% w/w and magnesium stearate in an amount that may vary from 0.5-5% w/w.

In various embodiments, the present invention is directed to a dispersible tablet comprising macitentan in the amount that may vary from 0.5-5% w/w, and the amount of β-mannitol may vary from 0.1-90% w/w. In various embodiments, the instant invention is directed to a dispersible tablet comprising macitentan in an amount that may vary from 0.5-5% w/w, β-mannitol in an amount that may vary from 0.1-90% w/w, and one or more of isomalt in an amount that may vary from 0.1-90% w/w, croscarmellose sodium in an amount that may vary from 5-20% w/w and magnesium stearate in an amount that may vary from 0.5-5% w/w.

In an embodiment, the present invention is notably directed to a dispersible tablet comprising 0.9-1.1% w/w macitentan, 67.5-82.5% w/w β-mannitol, 9-11% w/w of isomalt, 9.9-12.1% w/w of croscarmellose sodium, and 2.7-3.3% w/w of magnesium stearate, for example a dispersible tablet comprising 1% w/w macitentan, 75% w/w β-mannitol, 10% w/w of isomalt, 11% w/w of croscarmellose sodium, and 3% w/w of magnesium stearate.

In an embodiment, the instant invention is directed to a dispersible tablet comprising macitentan in an amount of about 1% w/w, β-mannitol in an amount of about 75% w/w, isomalt in an amount of about 10% w/w, croscarmellose sodium in an amount of about 11% w/w and magnesium stearate is present in an amount of about 3% w/w.

In various embodiments, macitentan is present in an amount of about 0.5-20% w/w.

In various embodiments, macitentan is present in an amount of about 1 mg, about 2.5 mg, about 3.5 mg or about 5.0 mg in the pharmaceutical composition or dispersible tablet.

In an embodiment, the instant invention wherein the mannitol is β-mannitol.

In an embodiment, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, wherein the β-mannitol grade is selected from Table 2 (below):

Table 2: Grades of β-mannitol

Mannitol grade	Particle size distribution	Specific surface area
Parteck® M200	D50 142-231 µm	3,0 m^2/g [Merck]
Pearlitol® SD100	D10-50-90: 64-111-165 µm	1.4 m^2/g [PreTaP] 0.6 m^2/g [Roquette]
Parteck® ODT	D50 70-120 µm	2,4 - 3,5 m^2/g [Merck]

In another embodiment, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, wherein the β-mannitol has a particle size distribution (PSD) such that, when measured according to the method entitled "Laser diffraction method for determining Particle Size Distribution" described in the "Methods" section below, the D10 value is from 10 to 60 µm, the D50 value is from 60 to 140 and the D90 value is from 140 to 220 µm. In particular, the β-mannitol used will have a maximum water content of 3%.

In another embodiment, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, wherein the β-mannitol has a specific surface area (SSA) of 2 m^2/g or less, and preferably of 0.5 to 1.5 m^2/g when measured according to the method entitled "BET method for determining Specific Surface Area" described in the "Methods" section below. In a further embodiment, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, wherein the β-

mannitol has a PSD such that, when measured according to the method entitled "Laser diffraction method for determining Particle Size Distribution" described in the "Methods" section below, the D10 value is from 10 to 60 μm, the D50 value is from 60 to 140 and the D90 value is from 140 to 220 μm, and wherein the β-mannitol has a SSA of 2 m^2/g or less, and preferably of 0.5 to 1.5 m^2/g when measured according to the method entitled "BET method for determining Specific Surface Area" described in the "Methods" section below. In particular, the β-mannitol used will have a maximum water content of 3%.

In another embodiment, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, comprising isomalt, wherein the isomalt wherein the PSD is such that the D90 is less than about 360 μm and the isomalt has a solubility of 42g per 100g solution in 20°C water.

In an embodiment, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, wherein β-mannitol is present in an amount of about 0.1-90% w/w.

In an embodiment, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, wherein isomalt is present in an amount of about 0.1-90% w/w.

In an embodiment, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, wherein croscarmellose sodium is present in an amount of about 5-20% w/w.

In an embodiment, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, wherein magnesium stearate is present in an amount of about 0.5-5% w/w.

In various embodiments, the instant invention is directed to a pharmaceutical composition, preferably a dispersible tablet, comprising macitentan in an amount of about 1% w/w, β-mannitol in an amount of about 75% w/w, and one or more of isomalt in an amount of about 10% w/w,

croscarmellose sodium in an amount of about 11% w/w and magnesium stearate in an amount of about 3% w/w.

In another embodiment, the pharmaceutical composition of the instant invention is in the form of a dispersible tablet.

In another embodiment, the dispersible tablet of the invention has a hardness of 20 to 120 N.

In another embodiment, the instant invention is directed to a method of treating pulmonary hypertension comprising administering to a patient in need thereof a macitentan pharmaceutical composition comprising macitentan, and β-mannitol.

In another embodiment, the instant invention is directed to a method of treating pulmonary hypertension comprising administering to a patient in need thereof a macitentan pharmaceutical composition comprising macitentan, and β-mannitol, and one or more of isomalt, croscarmellose sodium, and magnesium stearate.

In another embodiment, the instant invention is directed to a method of treating pulmonary hypertension, wherein the pulmonary hypertension is pulmonary arterial hypertension.

The formulations herein may be prepared by dry blending and compression into dispersible/chewable/swallowable/quick dissolving tablets as described notably in Lieberman, Lachman & Schwarz, "Pharmaceutical Dosage Forms: Tablets" (1989) . In one embodiment, the instant invention relates to a dispersible tablet as described above having a total weight of 500 mg or less which, when placed in a tablespoon containing 2-5 ml of water, preferably 3 ml of water, fully disperses in 5 min or less (and preferably in 2 min or less and more preferably in 1 min or less) when tested according to the method entitled "Disintegration on a spoon" described in the "Methods" section below.

The pharmaceutical compositions or dispersible tablets according to the invention may be used as medicaments.

The pharmaceutical compositions or dispersible tablets may be used for the preparation of medicaments for use in the treatment of pulmonary hypertension, in particular pulmonary arterial hypertension, or for use in the treatment of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients (especially in Fontan-palliated patients).

Pulmonary hypertension (PH) was reported for the first time in 1891 when the autopsy of a patient with sudden death revealed right ventricular hypertrophy and pulmonary artery sclerosis without any apparent cause. Pulmonary arterial hypertension (PAH) is a subgroup of PH and it is a progressive disease with elevated pulmonary vascular resistance (PVR) as the basic cause for increased right ventricular afterload and hypertrophy, which eventually proceeds to right ventricular dilatation and failure, and premature death. PH is clinically classified into five groups according to the World Health Organization (WHO) classification: pulmonary arterial hypertension (PAH) (group 1), PH related to left heart disease (group 2), PH due to lung disease and/or hypoxia (group 3), chronic thromboembolic PH and other pulmonary artery obstructions (group 4), and PH with unclear and/or multifactorial mechanisms (group 5) (Roger Hullin, *Cardiovascular Medicine* (2018), **21**(7–8):195–199; Simonneau et al., Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur. Respir. J.* (2018), Dec 13. pii: 1801913. doi: 10.1183/13993003.01913-2018. [Epub ahead of print]).

Concerning PAH, the present invention focuses on PAH which is haemodynamically characterized by the presence of a mean pulmonary artery pressure (PAP) > 20 mm Hg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg and a PVR of equal to or more than (>) 3 Wood units, alternatively > 2 Wood units, all measured at rest. In particular, the present invention focuses on PAH which is haemodynamically characterized by the presence of a mean pulmonary artery pressure (PAP) ≥ 25 mm Hg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg and a PVR of equal to or more than (>) 3 Wood units, alternatively > 2 Wood units, all measured at rest.

Functional single ventricular heart disease patients include both patients with hearts with only one ventricle and patients with hearts with two ventricles that are not amenable to biventricular repair (see Frescura and Thiene G. (2014), *Front Pediatr.* (2014), **2**, 62. The new concept of univentricular heart). Functional single ventricular heart disease patients include Fontan-palliated patients, that is, patients, typically children, with univentricular hearts or other related congenital heart diseases patients which have undergone the so-called Fontan procedure. The latter is a palliative surgical procedure that involves diverting the venous blood from the inferior vena cava (IVC) and superior vena cava (SVC) to the pulmonary arteries without passing through the morphologic right ventricle, i.e., the systemic and pulmonary circulations are placed in series with the functional single ventricle. The procedure was initially performed 1968 by Francis Fontan and Eugene Baudet. Contemporary modifications of surgical techniques have significantly improved survival. Overall, the Fontan patients have however decreased long-term survival, progressively deteriorating functional status and an increased risk of sudden death, which means that the procedure is considered to be palliative rather than curative (Fontan et al., *Circulation* (1990), **81**, 1520-1536).

Many post-Fontan complications arise as a result of increased venous pressure and congestion, and chronic low blood flow / cardiac output. Given the lack of ventricular force to drive blood flow through the pulmonary arteries, a low resistance (pulmonary vascular resistance [PVR]) and high capacitance system are mandatory for a well-functioning Fontan circuit. In the postoperative period, even small increases in PVR can lead to systemic venous hypertension associated with a decreased cardiac output despite a technically successful operation (Kirklin et al., *Eur. J. Cardiothorac. Surg.* (1990), **4**, 2-7). In fact, a slight increase in PVR at any time to levels that would be readily tolerated in normal physiology may result in progressive failure of the Fontan circulation. Importantly, high PVR is a strong predictor of mortality (Griffiths et al., *Ann. Thorac. Surg.* (2009), **88**, 558-563).

Compositions of this invention may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever

treatment of pulmonary hypertension, or of pulmonary vascular disease and/or cardiac dysfunction in functional single ventricular heart disease patients (especially in Fontan-palliated patients), is required.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and / or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

Definitions

As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term “about” when used before a numerical designation, e.g., pH, temperature, quantity, concentration and molecular weight, including range, indicates approximations which may vary by ±10%, ±5%, ±1%, or ±0.1%.

As used in the specifications and claims, the singular form “a”, “an” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a pharmaceutically acceptable carrier” may include a plurality of pharmaceutically acceptable carriers, including mixtures thereof.

The term “and/or” is intended to mean either or both of two components of the invention.

The term “subject,” “individual” or “patient’ is used interchangeably herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment. Preferably, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented.

The term “in need of treatment” and the term “in need thereof” when referring to treatment are used interchangeably and refer to a judgment made by a caregiver, e.g. physician, nurse, nurse practitioner, that a patient will benefit from treatment.

The term “pharmaceutically acceptable,” as used herein, refers to a component of a pharmaceutical composition that is compatible with the other ingredients of the formulation and not overly deleterious to the recipient thereof.

The term “therapeutically effective amount” as used herein, refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, or individual that is being sought by a researcher, healthcare provider or individual.

The term “w/w” as used herein, is intended to refer to mass fraction, i.e., the mass of a component divided by total mass of the whole. The term “% w/w” is intended to refer to the mass fraction multiplied by 100. Similarly, the term “w/v” refers to volume concentration, i.e., the mass of a component divided by total volume of the whole and the term “% w/v” refers to the volume concentration multiplied by 100.

The term “API” (Active Pharmaceutical Ingredient) as used herein, refers to a component in a therapeutic medication or nutraceutical substance that is biologically active.

The term “unit dose” refers to a single drug delivery entity, e.g., a tablet, capsule, dry powder, solution, dispersion etc., that is administered to an individual. The amount administered may vary according to numerous factors, including, e.g., the age of the individual, the weight of the individual, the genetic makeup of the individual, and the severity of symptoms exhibited by the individual to whom the drug is administered.

The unit dosage form (powder, granulation, tablet, sphere, or capsule) may be packaged into a blister foil pack, a stick pack, a sachet, a pouch, a bottle, or any other self-contained unit.

The term “excipient” as used herein is intended to mean components of a drug formulation other than the API that are added to a drug formulation to perform a specific function in the finished drug product. The excipient may aid

in dissolution or dispersion of the API, improve the taste profile of the drug product among other things. An excipient composition is intended to refer to a combination of a plurality of excipients that can be added to an API to produce a finished drug product.

The term "composition" as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The term "dispersible tablet", as used herein, is intended to mean a tablet which, when submitted to the disintegration method according to the European Pharmacopoeia version 10.4, disintegrates completely in water at 15-22°C in not more than 5 minutes, preferably less than 4 minutes or 3 minutes, and more preferably less than 2 minutes or even less than 1 minute.

The term "D10", as used herein, is intended to refer to a particle size distribution that, when measured according to the method entitled "Determination of particle size distribution by laser diffraction" described in the "Methods" section below, is such that at least 10% of the particles have a particle size lower than the D10 value mentioned. The term "D50", as used herein, is intended to refer to a particle size distribution that, when measured according to the method entitled "Determination of particle size distribution by laser diffraction" described in the "Methods" section below, is such that at least 50% of the particles have a particle size lower than the D50 value mentioned. The term "D90", as used herein, is intended to refer to a particle size distribution that, when measured according to the method entitled "Determination of particle size distribution by laser diffraction" described in the "Methods" section below, is such that at least 90% of the particles have a particle size lower than the D90 value mentioned.

The term "mannitol" as used herein refers to D-mannitol. Thus, "β-Mannitol", "δ-mannitol", "Beta-Mannitol" and "Delta-Mannitol" refer to the corresponding solid forms of D-mannitol.

The term "hardness" as used herein refers to tablet hardness or tablet breaking force as described in the European Pharmacopoeia version 10.4, and can be used as a measure of the cohesiveness of the ingredients of a tablet.

Examples of suitable pharmaceutical compositions and dispersible tablets are provided in the detailed descriptions which follow herein. One skilled in the art will recognize that the listing of said examples is not intended, and should not be construed, as limiting in any way the invention set forth in the claims which follow thereafter.

Abbreviations used in the specification, particularly the Schemes and Examples, are as listed in Table A, below.

Table A: Abbreviations

API		*Active Pharmaceutical Ingredient*
BU	=	Blend Uniformity
CU	=	Content Uniformity
DC	=	Direct Compression
LOQ	=	Limit Of Quantification
MgSt	=	Magnesium Stearate
PAH	=	Pulmonary Arterial Hypertension
WG	=	Wet Granulation

Compositions of macitentan of the present invention may be formulated according to the general schemes described below.

Process for the Preparation of Macitentan Dispersible Tablets:

The pharmaceutical compositions of Examples 1-4 were prepared according to a processes summarized by the flow charts shown in Figure 1 (wet granulation) and Figure 2 (direct compression) accordingly. Any

modifications from the flow charts are described in detail the respective Examples.

The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

Aspects of the present teachings may be further understood in light of the following examples, which should not be construed as limiting the scope of the present teachings in any way.

Example 1

Macitentan dispersible tablet manufacturing using DC with β-mannitol

Direct compression trials were performed comparing 3 grades of β-mannitol: Parteck® M200, Pearlitol® SD100 and Parteck® ODT. These granular and spray-dried forms β-mannitol grades are on the market claiming improved compressibility and fluidity as compared to standard crystalline β-mannitol. Since Parteck® ODT is a combination product of β-mannitol and sodium croscarmellose, the formula of batch 3 was adjusted to align the actual mannitol and sodium croscarmellose content with the other batches.

Table 2: Grades of β-mannitol

Mannitol grade	Particle size distribution	Specific surface area
Parteck® M200	D50 142-231 µm	3,0 m^2/g [Merck]
Pearlitol® SD100	D10-50-90: 64-111-165 µm	1.4 m^2/g [PreTaP] 0.6 m^2/g [Roquette]
Parteck® ODT	D50 70-120 µm	2,4 - 3,5 m^2/g [Merck]

Formulations

Table 3: Tablet formulations with different grades of β-mannitol

Material name:	Function	Amount per unit(mg)		
		Tablet 1	Tablet 2	Tablet 3
Macitentan	Active	0.5	0.5	0.5
Parteck® M200	Filler	38.4	-	-
Pearlitol® SD100	Filler	-	38.4	-
Parteck® ODT	Filler	-	-	40.6
Isomalt (GalenIQ® 721)	Compressibility enhancer	5.0	5.0	5.0
Croscarmellose sodium (AC-DI-SOL)	Disintegrant	5.60	5.6	3.4
Magnesium stearate	Lubricant	0.5	0.5	0.5
Total		50.0	50.0	50.0

Manufacturing procedure

Three batches of 6.4 kg scale of 0.5 mg strength were manufactured following an identical multi-step blending process. A geometrical blending approach was adopted for optimal blending efficiency. Macitentan (64g) was combined with mannitol (150 g) by Turbula® blending (20 min). Mannitol (250 g) was added by blending another 20 min Turbula® blending. The resulting premix was sieved (0.5 mm) in a bin containing mannitol (0.5 kg) followed by bin blending (35 min). The API:mannitol blend was sieved bin-to-bin (0.5 mm) followed by further blending (35 min). Mannitol (1 kg) was added and blended (35 min). The remaining mannitol, isomalt and sodium croscarmellose were added and blended (35 min). Finally, magnesium stearate was added by bin blending for 2 min. The resultant mixture was then compressed into 5 mm round tablets, at target hardness of 20N.

Results

Blend flowability was slightly superior for the batch using Parteck® M200 (1.7 s / 100 g) as compared to the batches with Pearlitol® SD100 (2.4 s / 100g) and Parteck® ODT (2.1 s / 100g) which can be attributed to the larger particle size of Parteck® M200. But all values can be considered decent. Further results of interest are summarized in Table 4. Batch homogeneity is best for Pearlitol® SD100, closely followed by Parteck® ODT. Both perform significantly better than Parteck® M200. Tablet parameters are similar, except for a shorter disintegration time for Parteck ODT. Yet, disintegration times are all < 1 minute (limit is 3 minutes). The most prominent difference can be noted after exposing the tablets to stressed conditions. After 28 days at 50°C 75% RH (the Compound A content has risen to 2% for Pearlitol® SD100, 4% for Parteck® M200 and even 6% for Parteck® ODT. Assay, purity and dissolution were similar across the batches (results not shown).

Table 4: Tablet parameters of batch formulations comprising different grades of β-mannitol.

Parameter	**Parteck® M200 Tablet 1**	**Pearlitol®SD100 Tablet 2**	**Parteck ODT Tablet 3**
Influence of mannitol grade on batch homogeneity			
BU, % RSD	4.1 %	2.8 %	1.7 %
CU, % RSD	1.8 %	1.5 %	1.5 %
CU weight corrected, % RSD	1.2 %	0.9 %	1.4 %
Influence of mannitol on tablet parameters			
Compression force	3.0 kN	3.0 kN	2.0 kN
Tablet hardness	38 N	33 N	33 N
Friability	0.3 %	0.3 %	0.2 %
Disintegration time	47 s	53 s	30 s
Tablet weight variation	1.3 %	1.1 %	0.7 %
Influence of mannitol on chemical stability			
% Compound A (28 days at 50°C 75% RH)	3.9 %	2.0%	6.0%

The stability data for the different batches is graphically illustrated in Figure 3. Figure 3 shows the amount of Compound A (hydrolysis degradation product of macitentan) with the tablets after storage conditions 50°C/ 10% relative humidity (RH) and 50°C/ 75% RH in comparison with the initial profile.

In conclusion, above results indicate DC (using Pearlitol® SD100) proves to be a promising alternative to WG (using δ-mannitol) for the preparation of macitentan dispersible tablets showing good batch homogeneity and acceptable tablet parameters and chemical stability.

Example 2

Comparison of Direct Compression Formulation over Wet Granulation Formulations

This experiment was performed to compare high shear wet granulation and direct compression processes and formulations to produce macitentan dispersible tablets on commercial production equipment. The DC formula (β-mannitol) and process show similar flowability, BU, tablet weight variation, friability, assay and dissolution rate as compared to the wet granulation formula (δ-mannitol) and process. The DC formula and process has advantage over wet granulation in terms of simplicity of formula and manufacturing process, excipient supply, compatibility of the blend and superior disintegration time. Overall, the process robustness of the novel formulation is superior to that formed via wet granulation.

Formulations

Table 5: Tablet formulations amounts for wet granulation and direct compression

	Tablet formula (mg/ unit)	
	Wet granulation	**Direct compression**
Inner phase		
Macitentan	0.5	-
Delta-mannitol (Parteck delta M)	29.5	-
Croscarmellose sodium	2.5	-
Isomalt GalenIQ 800	2.5	-
Outer phase		
Macitentan	-	0.5
mannitol (Pearlitol SD100)	9.0	38.4
Isomalt GalenIQ 721	2.5	5.0
Croscarmellose sodium	3.0	5.6
Magnesium stearate	0.5	0.5
SUM	50.0	50.0

Manufacturing Procedure (Wet Granulation)

One batch of Macitentan 0.5mg dispersible tablets using high shear granulation was produced at a batch size of 22.5 kg. Macitentan (0.225 kg), δ-mannitol (13.28 kg), croscarmellose sodium (1.13 kg) and isomalt (1.13 kg) were blended in high shear mixer (10 min) and subsequently granulated with purified water (3.15 kg). After passing through co-mill (9.5 mm screen) wet granules were dried in a fluid bed dryer at 70°C until a loss on drying of approx. 2% was reached. Dried granules were screened (1.0 mm) and blended with mannitol (4.05 kg), isomalt (1.13 kg) and croscarmellose sodium (1.35 kg) in bin blender (20 min). Finally, magnesium stearate was added by bin blending for 2 min. The resultant mixture was then compressed into 5 mm round tablets, at target hardness of 20N.

Manufacturing Procedure (Direct Compression)

One batch of Macitentan 0.5mg dispersible tablets using DC was produced at a batch size of 15 kg. Macitentan (150 g) was combined with mannitol (350 g) by Turbula® blending (20 min). The resulting premix added to a bin containing mannitol(7 kg). The Turbula® contained was rinsed with mannitol(0.5 kg) which was subsequently added to the bin followed by bin blending (35 min). The API:mannitol blend was sieved bin-to-bin (1 mm) followed by further blending (35 min). The remaining mannitol, isomalt and sodium croscarmellose were added and blended (35 min). Finally, magnesium stearate was added by bin blending for 2 min. The resultant mixture was then compressed into 5 mm round tablets, at target hardness of 20N.

Results

Flowability, tablet weight variation and BU of both batches are in line, indicating similar processability and homogeneity can be obtained with both formulations and manufacturing processes. A clear difference can however be observed in compactibility of both blends. The compression force - hardness profiles generated (See Figure 4a) show that higher tablet hardness is achieved at lower compression forces for the DC formula. This elevated tablet hardness however does not affect the disintegration time of the tablets (See Figure 4b). Macitentan tablets are dispersible tablets which implicates a compendial disintegration time limit of only 3 minutes. Hence, the balance between tablet hardness and disintegration time is a challenge in dispersible tablet compression. Sufficient tablet hardness is required to minimize tablet friability and avoid tablet defects during handling, shipment or packaging. On the other hand, there is a risk of disintegration time failure when tablet hardness is increased. Therefore, a superior hardness- disintegration time profile is beneficial to process robustness. Disintegration times of the 0.5 mg tablets (50 mg tablet weight) of both batches are well below the 3-minute limit yet the difference will become more pronounced at higher tablet weight. At 750 mg

tablet weight and a comparable disintegration time of approx.2 minutes the tablet hardness of the DC formula is 143N as compared to only 80N for wet granulation. The difference between both processes is even more pronounced when the dispersion time of the tablets on a spoon is compared. Patients are instructed to administer the drug product dispersed in a little water on a spoon. Tablets produced by DC disperse within 1 minute on a teaspoon with 3 ml water, whereas for the wet granulation tablets full dispersion takes about 4 minutes under the same conditions. Limited differences were observed with respect to assay, purity, CU, BU and dissolution (See Figure 4c).

Table 6: Blend and tablet parameters for wet granulation and direct compression batches.

Parameter	Wet granulation	DC
Final		
Flowability (s/100 g)	1.9	2.2
BU, RSD (%)	2.5	2.0
Tablet		
Pre-Compression force (kN)	1.0	0.0
Compression force (kN)	**5.0**	**3.5**
Weight variation (%)	1.17	0.96
Hardness (N)	17	21
Friability (%)	0.4	0.3
Disintegration time (s)	**63**	**27**
Dispersion on a spoon (min)	**4**	**1**
CU, RSD (%)	1.8	1.7
Assay (%)	96.4	97.3
Purity (Compound A) (%)	0.11	< LOQ

Figures 4a-4c depict results from the comparison of the wet granulation and direct compression formulations. Based on these results there are no major benefits from the use of δ-mannitol/wet granulation. By smart selection of the β-mannitol grade in combination with DC process, the product robustness can be enhanced while delivering drug product with comparable quality attributes

The results indicate direct compression using Pearlitol® SD100 proves to be a suitable alternative to wet granulation for the preparation of macitentan

dispersible tablet showing good batch homogeneity and acceptable tablet parameters and chemical stability.

Example 3

Optimization of novel macitentan formula (lubricant level)

During manufacturing of macitentan dispersible tablets of 2.5 mg and 3.5 mg dose strengths comprising 1% magnesium stearate, picking defects in tablet inscriptions were observed. After extensive investigation, the problem was resolved without major impact on the tablet characteristics by increasing the magnesium stearate content in the composition up to 3%. Analytical data proved the magnesium stearate increase did not impact the dissolution rate of the macitentan dispersible tablets significantly.

Formulations

Table 7: Macitentan 2.5 mg dispersible tablet formulation.

Material name:	Macitentan 2.5 mg dispersible tablets					
	1 % MgSt		2 % MgSt		3 % MgSt	
	mg	%	mg	%	mg	%
Macitentan	2.50	1.0	2.50	1.0	2.50	1.0
Mannitol (Pearlitol ® 100 SD)	192.00	76.8	189.50	75.8	187.00	74.8
Isomalt (GalenIQ® 721)	25.00	10.0	25.00	10.0	25.00	10.0
Croscarmellose sodium (AC-DI-SOL)	28.00	11.2	28.00	11.2	28.00	11.2
Magnesium stearate	**2.50**	**1.0**	**5.00**	**2.0**	**7.50**	**3.0**

Manufacturing procedure

Three batches of Macitentan 2.5mg dispersible tablets using DC were produced at a batch size of 6.4 kg. Macitentan (64 g) was combined with mannitol (200 g) by Turbula® blending (20 min). The resulting premix added to a bin containing mannitol(2 kg). The Turbula® contained was rinsed with mannitol (0.5 kg) which was subsequently added to the bin followed by bin blending (15 min). The remaining mannitol, isomalt and sodium croscarmellose were added and blended (15 min). Finally, magnesium stearate was added by bin blending for 2 min. The resultant mixture was then compressed into 9 mm round tablets, at target hardness of 40N.

Results

To investigate whether the level of lubricant in the formula (1%) was sufficient, Macitentan 2.5 mg dispersible tablet batches with increased magnesium stearate level (2% and 3%) were manufactured. There was a definite improvement with increased magnesium stearate concentration eliminating picking in tablets completely at a level of 3%. The increase in magnesium stearate did not impact tablet weight variation, hardness, friability or disintegration time nor did it impact on the dissolution the macitentan dispersible tablets (Figure 5). Furthermore, no impact on BU, CU, assay and purity was observed (results not shown).

Table 8: Tablet parameters of formulations comprising different Magnesium Stearate amounts.

Parameter	**1% Magnesium stearate**	**2% Magnesium stearate**	**3% Magnesium stearate**
Pre-Compression force [kN]	1.0	1.0	1.0
Compression force [kN]	5.6	5.5	6.5
Tablet appearance	Sticking defects	Light sticking defects	No sticking defects
Weight variation (%)	2.0	1.4	1.9
Hardness (N)	43	39	46
Friability (%)	0.3	0.3	0.3
Disintegration time (s)	106	90	88

Example 4

Macitentan dispersible tablets of 1 mg, 2.5 mg and 3.5 mg dose strengths

Macitentan dispersible tablets of 1 mg, 2.5 mg and 3.5 mg dose strengths, comprising 3% magnesium stearate, were manufactured to confirm formulation and manufacturing process for different strengths.

Formulations

Table 9: Macitentan 1.0 mg, 2.5 mg and 3.5 mg dispersible tablets formulations.

Material name	Macitentan dispersible tablets			
	%	mg		
		1 mg dose	2.5 mg dose	3.5 mg dose
Macitentan	1.0	1.0	2.5	3.5
Mannitol (Pearlitol 100 SD)	75.0	75.0	187.5	262.5
Isomalt (GalenIQ 721)	10.0	10.0	25.0	35
Croscarmellose sodium (AC-DI-SOL)	11.0	11.0	27.5	38.5
Magnesium stearate	3.0	3.0	7.5	10.5

Manufacturing procedure

Three batches of Macitentan dispersible tablets using DC were produced at a batch size of 15 kg. Macitentan (150 g) was combined with mannitol (350 g) by Turbula® blending (20 min). The resulting premix added to a bin containing mannitol (7 kg). The Turbula® container was rinsed with mannitol (0.5 kg) which was subsequently added to the bin followed by bin blending (45 min). The remaining mannitol, isomalt and sodium croscarmellose were added and blended (20 min). Finally, magnesium stearate was added by bin blending for 2 min. The resultant mixture was then placed on a rotary tablet press. Different punch sets were used to allow for differentiation across the strengths.

Results

Macitentan dispersible tablets share a common blend which is compressed dose proportionally to obtain different tablet strengths. Blend homogeneity is passing the acceptance criterium of SD ≤ 3.0% very well and shows little inter-batch variability. Tablet parameters and content uniformity were good for the different tablet sizes and shapes. Similar dissolution profiles were obtained across the different strengths (Figure 6).

Table 10: Blend and tablet parameters for Macitentan dispersible tablets of 1.0, 2.5 and 3.5 mg dose strength.

Parameter	1.0 mg Dose	2.5 mg Dose	3.5 mg Dose
BU, SD (%)	1.4	1.0	0.7
Punch	Oval, 8x5mm	Round, 9mm	Oval, 9x5.5mm
Pre-Compression force [kN]	3	1	2
Compression force [kN]	7	7	12
Tablet appearance	Ok	Ok*	Ok
Weight variation (%)	0.85	0.70	0.64
Hardness (N)	50	43	80
Friability (%)	0.2	0.2	0.1
Disintegration time (s)	64	65	104
CU, RSD (%)	1.0	1.0	1.6

* About 1% tablets with small edge chipping defects observed yet this was resolved by increasing the hardness for subsequent batches.

Methods

The tests for flowability, tablet hardness, friability, disintegration time were conducted as described in the European Pharmacopoeia version 10.4.

Flowability: ISO Lab flow funnel, method according to European Pharmacopoeia version 10.4

Tablet hardness: Sotax® HT1 hardness tester (Experiments 1 and 3), Schleuniger 8M® (experiment 2)

Friability: Sotax® FT2 friabilator, method according to European Pharmacopoeia version 10.4, 2.9.7. **Friability** of Uncoated Tablets)

Disintegration time: Sotax® DT2 disintegration tester, method according to European Pharmacopoeia version 10.4, Monograph Tablets (0478) for dispersible tablets (Dispersible tablets disintegrate within 3 minutes when examined by 5.3 Disintegration test for tablets and capsules, but using water R at 15–25° C.)

Disintegration on a spoon: A tablet is put on a tablespoon and 3 ml water is added. Dispersion is examined by gently touching the tablet mass with a spatula. Full dispersion is achieved when no hard mass is left.

Assay/purity

The HPLC conditions for measuring the assay, purity and tablet content data in Figure 3 and Tables 4, 6, and 10 were as follows:

Diluent:

Solution A: dissolve 1.6 g ammonium bicarbonate in 1000 ml de-ionized water and bring to pH 9 with ammonium hydroxide solution

Solution B: acetonitrile

Combine 500 ml of solution A with 500 ml of solution B and mix

Mobile Phases:

Mobile phase A: Acetonitrile/di-ionized Water/Trifluoroacetic, 500/500/5 ml

Mobile phase B: Acetonitrile/di-ionized Water/Trifluoroacetic acid, 650/350/5 ml

Operating Parameters:

Table 11: Gradient Program

Time (Minutes)	Mobile Phase A (% vol.)	Mobile Phase B (% vol.)	Flow (ml/min)
0	100	0	1.0
12	100	0	1.0
42	65	35	1.0
42.1	100	0	1.0
50	100	0	1.0

- Column: Nucleosil® C18 HD, EC 250/4 100-5, 250 mm length x 4.0 mm i.d., 5 µm particle size
- Detection: UV
- Wavelength: 260 nm, 4 nm
- Column Temperature: 25 °C
- Auto-Sampler Temperature: 5°C
- Analysis Run Time: 50 minutes
- Injection volume: 80 µl (injected amount = 4 µg)
- Retention time macitentan: 21 min
- Relative retention time Compound A: 0.22 (reference: Macitentan)

Dissolution test

The analytical method used to obtain dissolution test results in Figures 4c, 5 and 6 is summarized in Table 12:

Table 12: Dissolution Testing Parameters

Parameter	Value
Apparatus	Paddle (USP type 2, Ph. Eur. JP)
Dissolution medium	0.05 M sodium phosphate buffer pH 6.8 with 0.5% cremophor A25
Medium temperature	37.0 ± 0.5 °C
Medium volume	500 ml (0.5 mg dose strength) 900 ml (other dose strengths)
Paddle rotation speed	50 rpm
Sampling time points	5, 10, 15, 30, 45, 60 min
Sample filter	Glass fiber (e.g. Gelman, 1 µm)
Analytical finish	HPLC with UV detection at 260 nm

The HPLC conditions for measuring the macitentan content in the samples were as follows:

Diluent

Solution A: dissolve 1.6 g ammonium bicarbonate in 1000 ml de-ionized water and bring to pH 9 with ammonium hydroxide solution

Solution B: acetonitrile

Combine 500 ml of solution A with 500 ml of solution B, mix well and degas before use.

Mobile Phase:

Mobile phase A: Combine 850 ml acetonitrile, 150 ml water and 5 ml trifluoroacetic acid, mix well and degas before use

Chromatographic conditions:

- Column: EC 250/3 Nucleodur® C18 gravity 3µm, 250 mm length x 3.00 mm i.d., 3 µm particle size
- Detection: UV
- Wavelength: 260 nm
- Column Temperature: 25 °C
- Auto-Sampler Temperature: 5°C
- Mobile phase: Isocratic mode
- Flow rate: 0.5 ml/min
- Analysis Run Time: 10 minutes
- Injection volume: 100 µl

Laser diffraction method for determining Particle Size Distribution

The Particle Size Distribution of a sample is determined via dry dispersion laser diffraction by dry measurements performed on 10 g of powder using the apparatus Mastersizer 2000 (Malvern Instruments, Worcestershire, UK) and the Sirocco 2000 dry dispersion unit. The test is performed in triplicate and averages are calculated using the Malvern software. The applied instrument parameters for this method are described in Table 13 hereafter:

Table 13: Dry Dispersion Laser Diffraction Parameters

Parameter	Value
Instrument	Mastersizer 2000 (Malvern Instruments, Worcestershire, UK)
Method	Frauenhofer
Models	General purpose; Normal
Measurement time	30 s
Background time	30 s
Lower obscuration limit	0.2
Upper obscuration limit	25
Obscuration filter	1 min time-out
Sample tray	General purpose
Vibration rate	50%
Dispersive air pressure	2 bar
Aliquots	1

BET method for determining Specific Surface Area

The Specific Surface Area of a solid sample is tested using the method described using the standardized method ISO 9277:2010 thanks to the measurement of the amount of physically adsorbed gas according to the Brunauer, Emmett and Teller (BET) method. The adsorption analysis with nitrogen as adsorptive is recorded at 77 K on a Micromeritics® TriStar II 3020 surface area analyzer, with a relative pressure from $p_0/p = 0.01$ to $p_0/p = 0.30$. Prior to the actual adsorption investigations, the samples are pre-treated at 300 °C in vacuum for 16 hours. The dry sample mass obtained after that pre-treatment is used in the various calculations performed according to ISO 9277:2010.

Example 5

Macitentan dispersible tablets of 2.5 mg dose strength: formula variation

Macitentan dispersible tablets of 2.5 mg dose strength with varying levels of disintegrant and lubricant were manufactured to confirm formulation robustness. For Tablet 2 the croscarmellose sodium level was reduced by 50%, resulting in a croscarmellose sodium concentration of 5.5%. For Tablet batch 3 the magnesium stearate level was increased to 5% of the formulation. These differences in formulation were compensated by changes in mannitol amount so that the resulting tablet weight remained at 250 mg.

Table 14: 2.5 mg Tablet Formulations

Material name:	**Function**	**Amount per unit(mg)**		
		Tablet 1 Reference	**Tablet 2 Reduction disintegrant**	**Tablet 3 Increased lubricant**
Macitentan	Active	2.50	2.50	2.50
Beta-mannitol (Pearlitol® SD100)	Filler	187.50	**201.25**	**182.50**
Isomalt (GalenIQ® 721)	Filler - Compressibility enhancer	25.00	25.00	25.00
Croscarmellose sodium (AC-DI-SOL®)	Disintegrant	27.50	**13.75**	27.50
Magnesium stearate	Lubricant	7.50	7.50	**12.50**
Total		250.00	250.00	250.00

Manufacturing procedure

Three batches of Macitentan dispersible tablets using DC were produced at a batch size of 1.5 kg. Macitentan (15 g) was combined with mannitol (35 g) by Turbula® blending (20 min). The resulting premix added to a bin containing mannitol (0.7 kg). The Turbula® container was rinsed with mannitol (0.05 kg)

which was subsequently added to the bin followed by bin blending (45 min). The remaining mannitol, isomalt and sodium croscarmellose were added and blended (20 min). Finally, magnesium stearate was added by bin blending for 4 min. The resultant mixture was then compressed on a rotary tablet press.

Results

Tablet parameters and content uniformity were good for the different tablet batches that were obtained, indicating the tablet formulation robustness.

Table 15

Parameter	Tablet 1 Reference	Tablet 2 Reduction disintegrant	Tablet 3 Increased lubricant
Tablet appearance	Ok	Ok	Ok
Weight variation (%)	1.06	0.65	1.25
Hardness (N)	72	70	67
Friability (%)	0.2	0.2	0.2

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

Throughout this application, various publications are cited. The disclosure of these publications is hereby incorporated by reference into this application to describe more fully the state of the art to which this invention pertains.

We Claim:

1. A pharmaceutical composition comprising:
    a. macitentan or a pharmaceutically acceptable salt, solvate, hydrate or morphological form thereof,
    b. β-mannitol,
    c. isomalt,
    d. croscarmellose sodium, and
    e. magnesium stearate.

2. The pharmaceutical composition of claim 1, wherein macitentan is present in an amount of about 0.5-20 % w/w.

3. The pharmaceutical composition of claim 1 or 2, wherein the macitentan is present in an amount of about 1 mg, about 2.5 mg, about 3.5 mg or about 5 mg.

4. The pharmaceutical composition of any of claims 1 to 3, wherein the β-mannitol has a maximum water content of 3% and the particle size distribution of the β-mannitol is such that the D10 value is from 10 to 60 µm, the D50 value is from 60 to 140 and the D90 value is from 140 to 220 µm .

5. The pharmaceutical composition of claim 4, wherein the β-mannitol is present in an amount of about 0.1-90% w/w.

6. The pharmaceutical composition of any of claims 1 to 5, wherein the isomalt is present in an amount of about 0.1-90% w/w.

7. The pharmaceutical composition of claim 6, wherein the particle size distribution of the isomalt is such that the D90 is less than about 360 µm and the isomalt has a solubility of 42g per 100g solution in 20°C water.

8. The pharmaceutical composition of any of claims 1 to 7, wherein the croscarmellose sodium is present in an amount of about 5-20% w/w.

9. The pharmaceutical composition of any of claims 1 to 8, wherein the magnesium stearate is present in an amount of about 0.5-5% w/w.

10. The pharmaceutical composition of claim 1, wherein the macitentan is present in an amount of about 1% w/w, the β-mannitol is present in an amount of about 75% w/w, the isomalt is present in an amount of about 10% w/w, the croscarmellose sodium is present in an amount of about 11% w/w and the magnesium stearate is present in an amount of about 3% w/w.

11. The pharmaceutical composition of any of claims 1 to 10, wherein the composition is a dispersible tablet.

12. The pharmaceutical composition of any of claims 1 to 11, prepared by direct compression process.

13. The pharmaceutical composition of any of claims 1 to 12, having a hardness of 20-120 N.

14. A method of treating pulmonary hypertension comprising administering to a patient in need thereof the pharmaceutical composition of any of claims 1 to 13.

15. The method of claim 14, wherein the pulmonary hypertension is pulmonary arterial hypertension.

16. A dispersible tablet comprising:

a. about 0.5-20 w/w macitentan,
b. about 0.1-90% w/w mannitol,
c. about 0.1-90% w/w of isomalt,
d. about 5-20% w/w of croscarmellose sodium, and
e. about 0.5-5% w/w of magnesium stearate.

17. The dispersible tablet of claim 16, wherein macitentan comprises an amount of about 1 mg, about 2.5 mg, about 3.5 mg or about 5 mg.

18. The dispersible tablet of claim 16 or 17, wherein mannitol is β-mannitol.

19. The dispersible tablet of claim 18, wherein the β-mannitol has a maximum water content of 3% and the particle size distribution of the β-mannitol is such that the D10 value is from 15 to 60 µm, the D50 value is from 105 to 125 and the D90 value is from 155 to 215 µm.

20. The dispersible tablet of any of claims 16 to 19, wherein the particle size distribution of the isomalt is such that the D90 is less than about 360 µm and the isomalt has a solubility of 42g per 100g solution in 20°C water.

21. The dispersible tablet of any of claims 16 to 20, prepared by direct compression process.

22. A method of treating pulmonary hypertension comprising administering to a patient in need thereof a dispersible tablet of any of claims 16 to 21.

23. The method of claim 22, wherein the pulmonary hypertension is pulmonary arterial hypertension.

24. A process for preparing the dispersible tablet of any of claims 16 to 21.

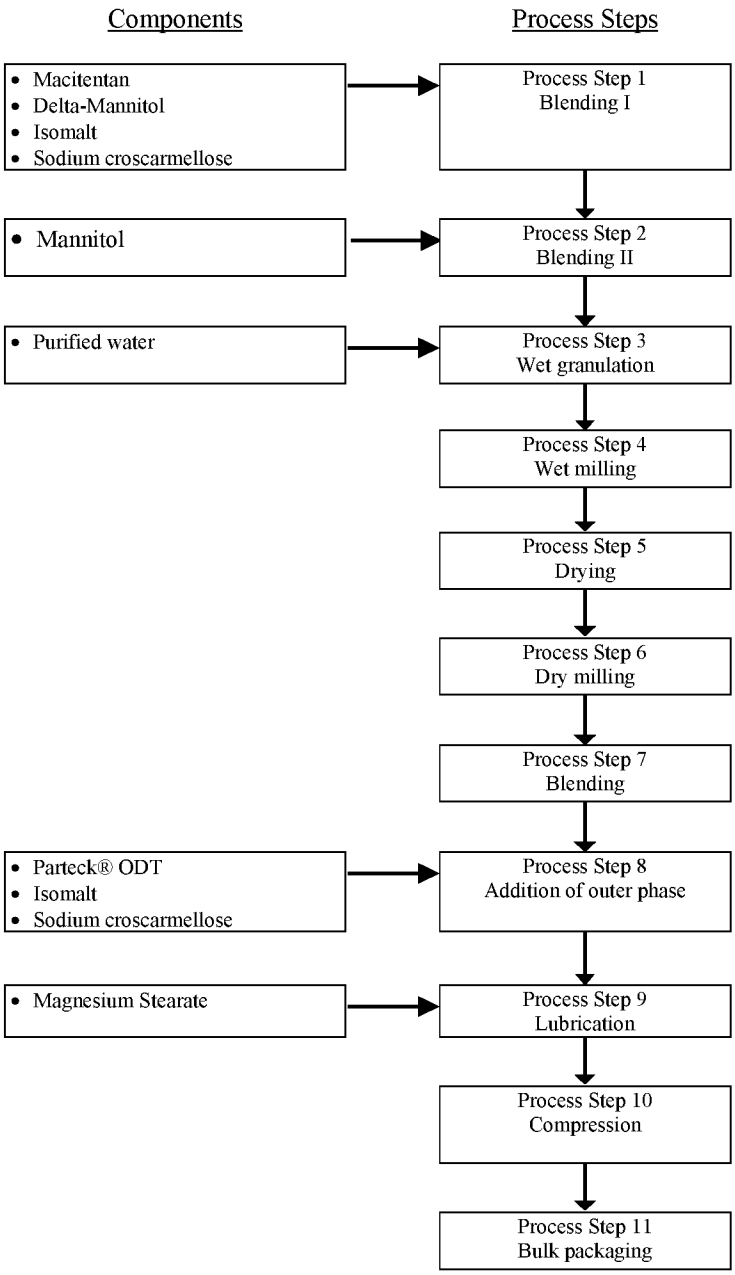

Components
Process Steps
• Macitentan
• Delta-Mannitol
• Isomalt
• Sodium croscarmellose
Process Step 1
Blending I
• Mannitol
Process Step 2
Blending II
• Purified water
Process Step 3
Wet granulation
Process Step 4
Wet milling
Process Step 5
Drying
Process Step 6
Dry milling
Process Step 7
Blending
• Parteck® ODT
• Isomalt
• Sodium croscarmellose
Process Step 8
Addition of outer phase
• Magnesium Stearate
Process Step 9
Lubrication
Process Step 10
Compression
Process Step 11
Bulk packaging

Figure 1

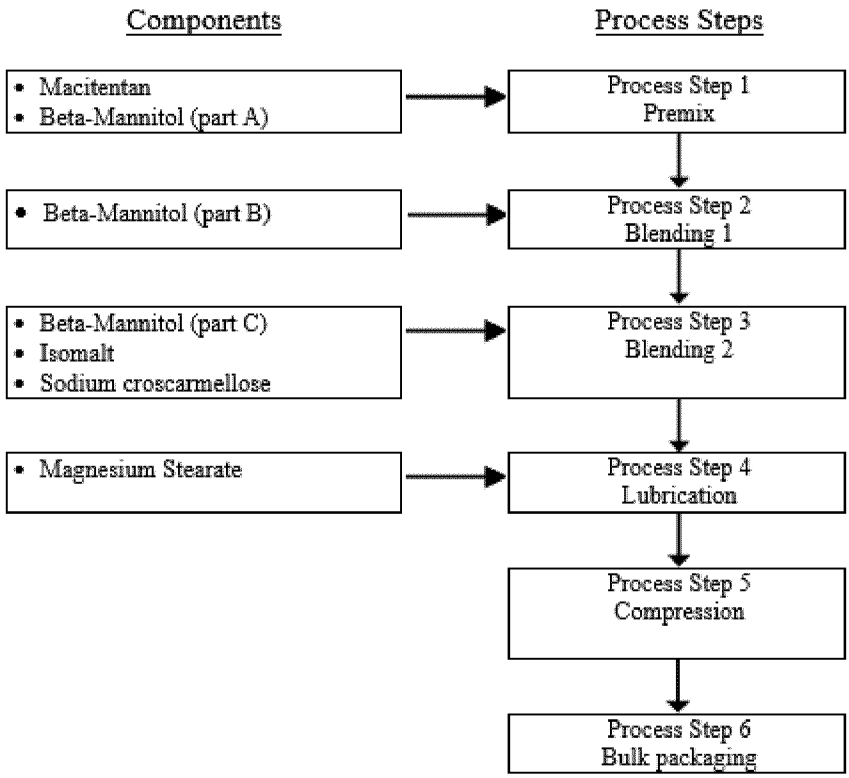


Figure 2

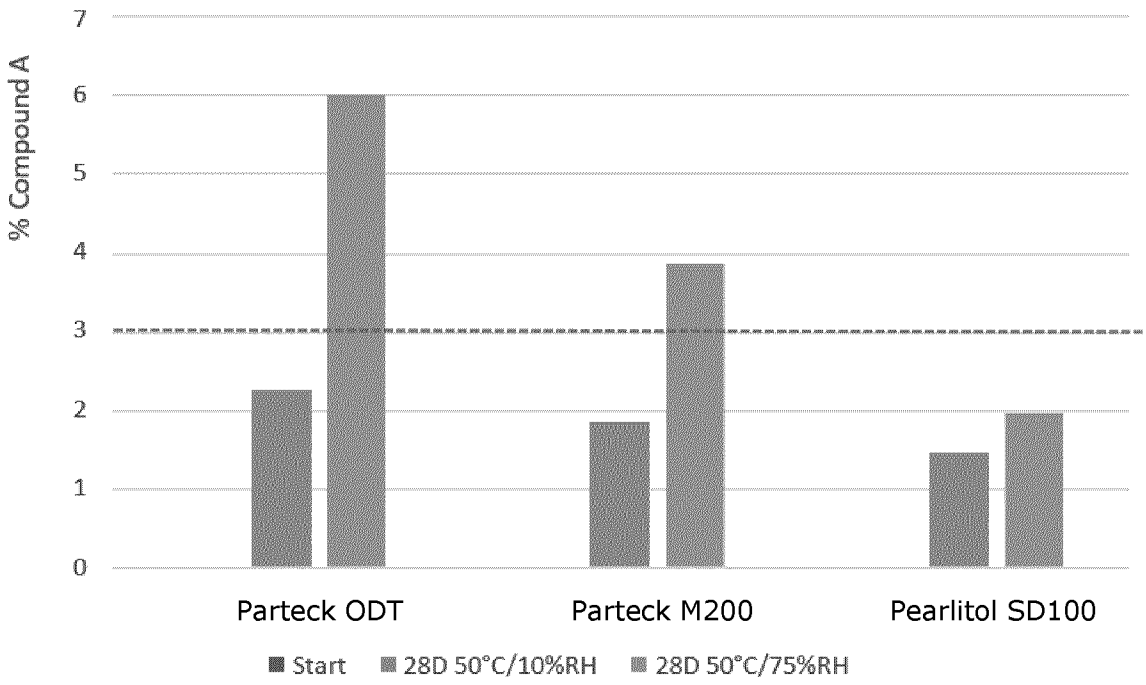


Figure 3

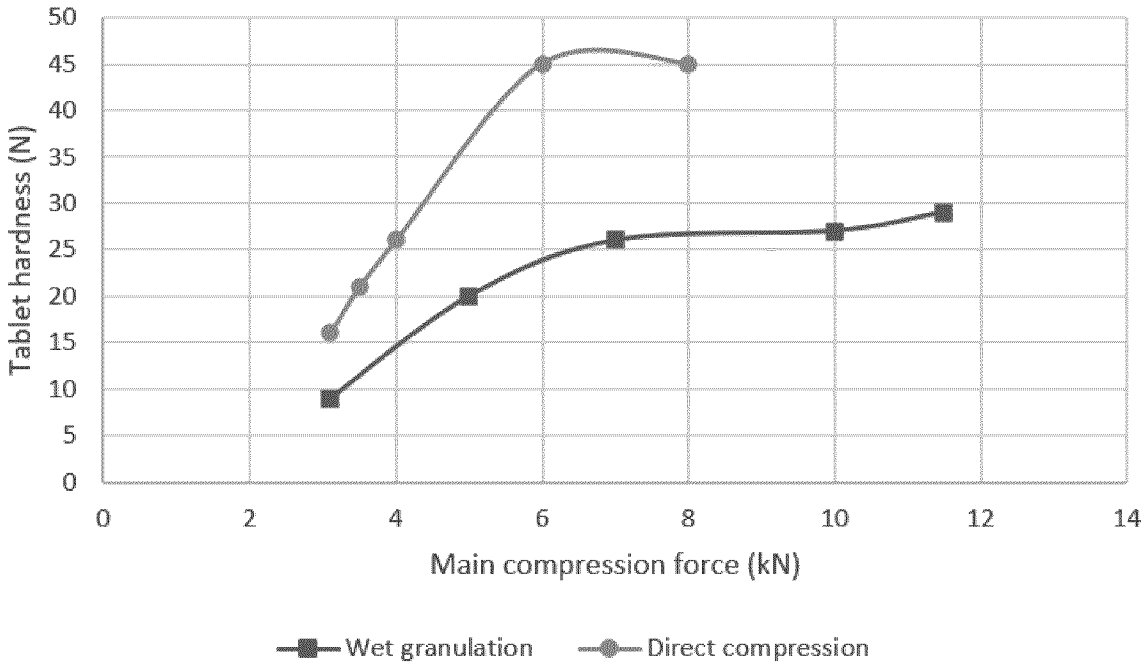


Figure 4a

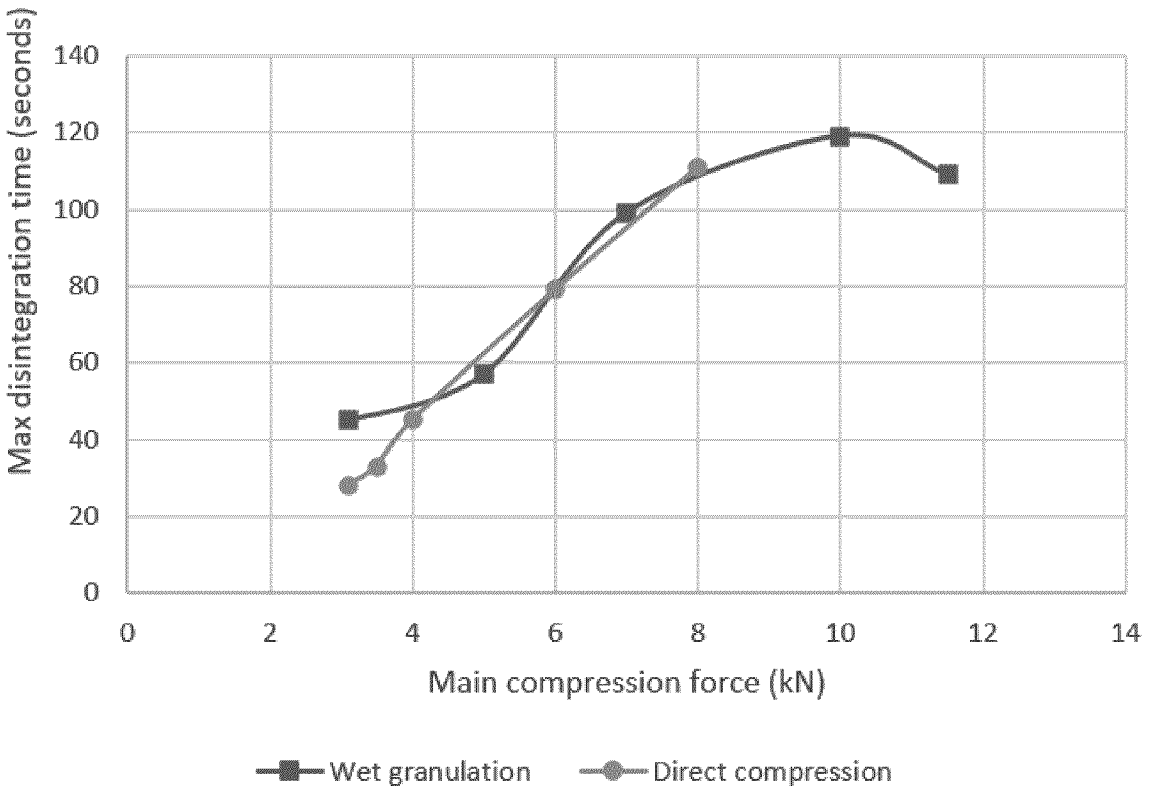


Figure 4b

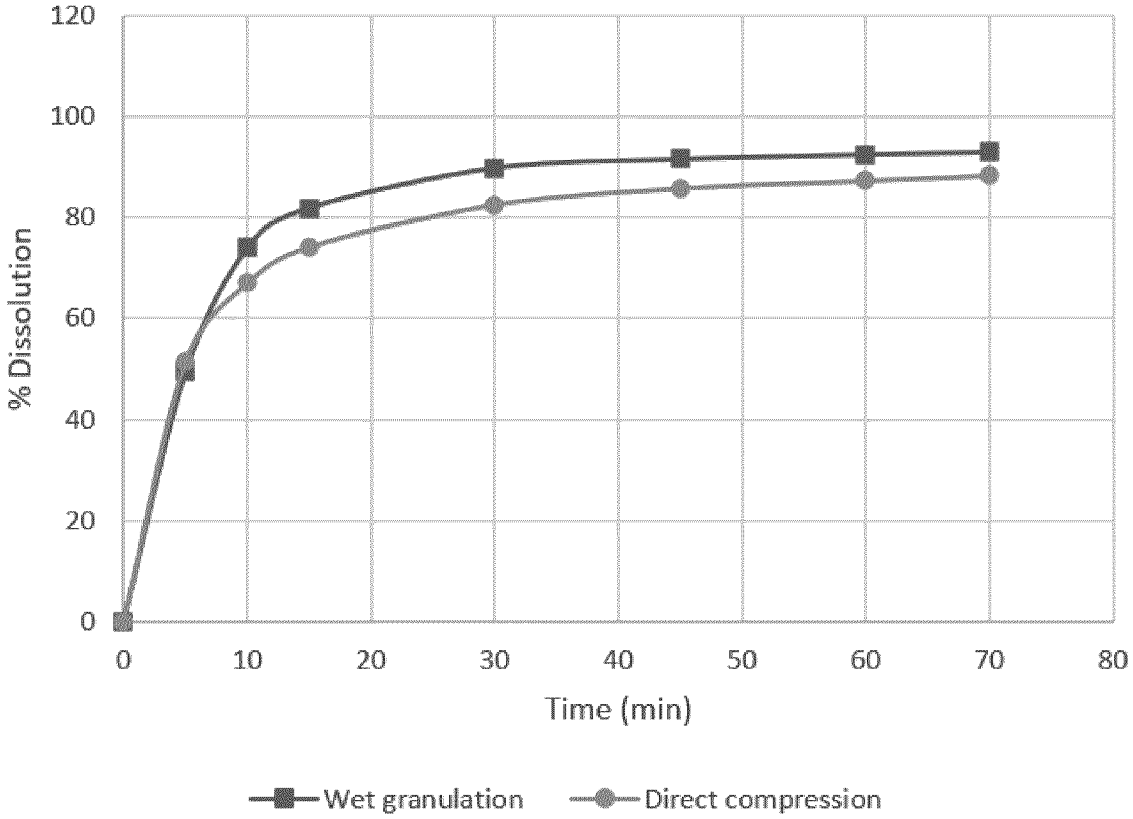

120
100
80
60
40
20
0
% Dissolution
0
10
20
30
40
50
60
70
80
Time (min)
Wet granulation
Direct compression

Figure 4c

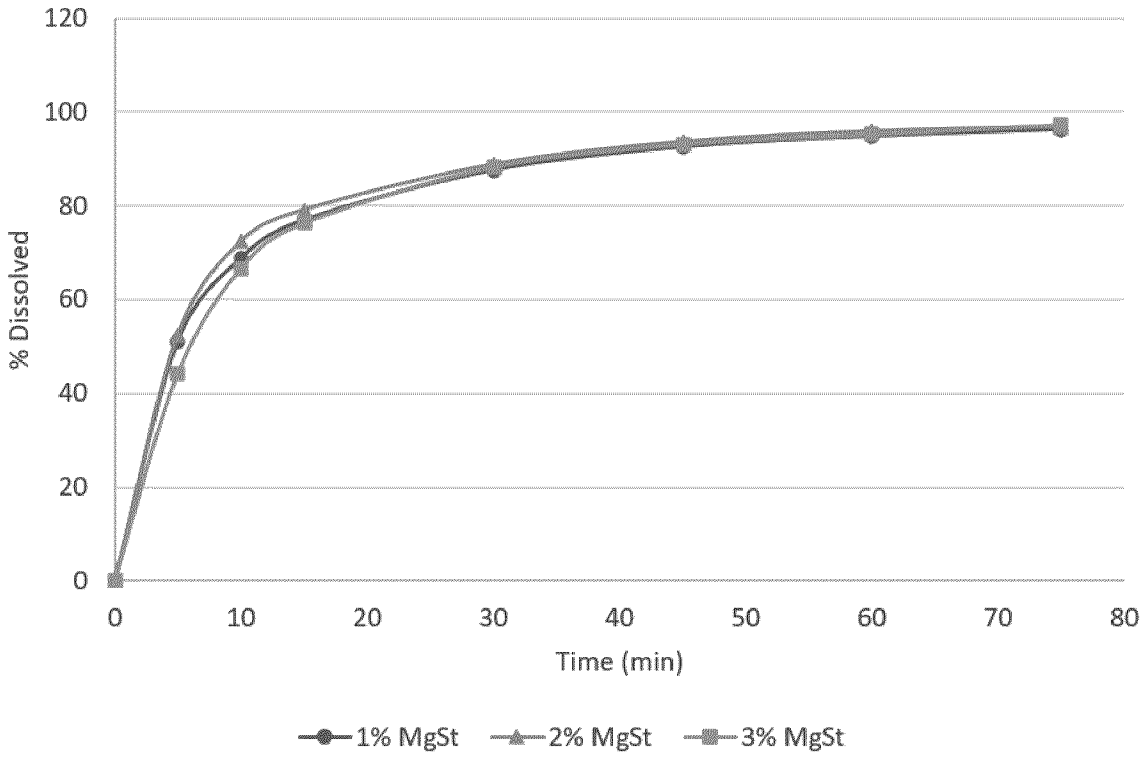

120
100
80
60
40
20
0
% Dissolved
0
10
20
30
40
50
60
70
80
Time (min)
1% MgSt
2% MgSt
3% MgSt

Figure 5

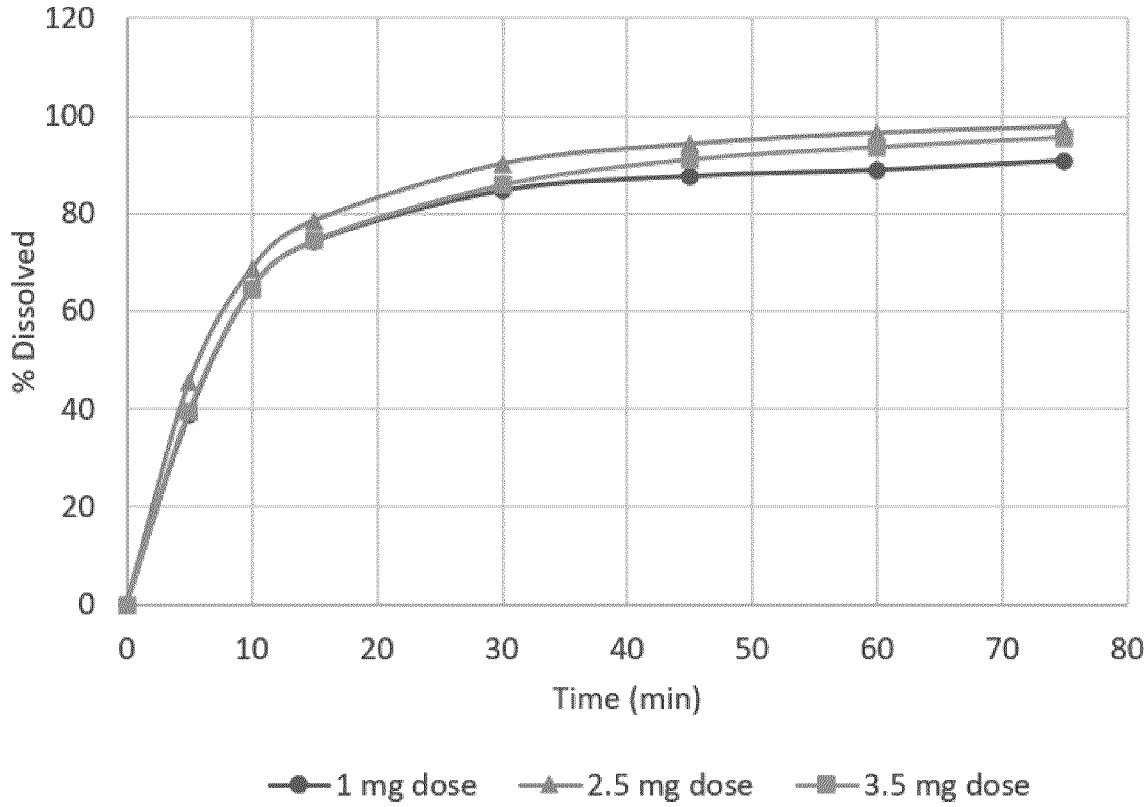

120
100
80
60
40
20
0
% Dissolved
0
10
20
30
40
50
60
70
80
Time (min)
1 mg dose
2.5 mg dose
3.5 mg dose

Figure 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/065797

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/00 A61K31/506 A61P9/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 September 2022	06/10/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Madalinska, K

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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6

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Information on patent family members

International application No
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