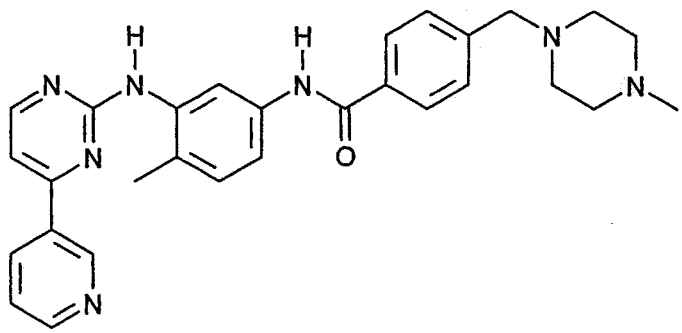
High drug load tablet

The present invention relates to pharmaceutical tablets comprising 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide or pharmaceutically acceptable salts thereof and is hereinafter referred as Compound I.

Compound I has the formula (1)



(1)

Compound I free base and its acceptable salts thereof are disclosed in the European Patent application 0564409. Compound I mesylate and Compound I mesylate alpha and beta crystal forms are disclosed in International Patent application WO 99/03854.

Typically, prescribed daily dosages of Compound I mesylate for the treatment of leukemia are high, e.g. 400 - 800 mg in adults. Thus, there is a need for an oral dosage form which is convenient to administer and provides a daily dosage amount of Compound I.

Accordingly, the present invention provides a tablet with high drug loading comprising a pharmacologically effective amount of Compound I or a pharmaceutically acceptable salt thereof present in an amount of from about 30% to 80%, e.g. at least about 35, 40, 45, 50 or 55% to about e.g. 60, 65, 70, 75 or 80%, preferably more than 55%. In particular, the amount of Compound I may vary from 45 to 80%, e.g. 50 to 70% in weight based on the total weight of the tablet.

Compound I may be in the free base form or pharmaceutically acceptable salts thereof, e.g. monomesylate form. The active moiety corresponds to Compound I in the free base form. For example, 119.5 mg of Compound I mesylate salt correspond to 100 mg of Compound I free base active moiety.

The present invention also provides a tablet comprising
(a) a pharmacologically effective amount of Compound I, and
(b) at least one pharmaceutically acceptable excipient suitable for the preparation of tablets wherein the amount of Compound I or pharmaceutically acceptable salt thereof, calculated as the percentage of the content in weight of the active moiety based on the total the tablet, is from about 30% to 80%, e.g. at least about 35, 40, 45, 50 or 55% to about e.g. 60, 65, 70, 75 or 80%, preferably more than 55%. In particular the amount of Compound I may vary from 45 to 80%, e.g. 50 to 70% in weight of the active moiety based on the total weight of the tablet.

In another aspect, the present invention provides a tablet wherein the Compound I is in crystalline form.

In a further aspect of the invention, the monomesylate salt of Compound I is used.

In a preferred embodiment of the invention, the monomesylate salt of Compound I is in crystalline form, e.g. alpha or beta crystal form, most preferably, the monomesylate salt of Compound I is in the beta crystal form.

One or more pharmaceutically acceptable excipients may be present in the tablets, e.g. those conventionally used, e.g. (1.1) at least one binder, e.g. microcrystalline cellulose, hydroxypropylmethyl cellulose, (1.2) at least one disintegrant, e.g. cross-linked polyvinylpyrrolidinone, e.g. Crospovidone®, (1.3) at least one glidant, e.g. colloidal silicon dioxide, (1.4) at least one lubricant, e.g. magnesium stearate and/or (1.5) basic coating. In the tablet according to the present invention, microcrystalline cellulose is used as a binder.

Reference is made to the extensive literature on the subject for these and other excipients and procedures mentioned herein, see in particular Handbook of Pharmaceutical Excipients, Third Edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, USA and Pharmaceutical Press, London; and Lexikon der Hilfsstoffe für Pharmazie, Kosmetik and angrenzende Gebiete edited by H.P. Fiedler, 4th Edition, Edito Cantor, Aulendorf and earlier editions which are incorporated herein by reference.

Binders (1.1) include but are not restricted to starches, e.g. potato, wheat or corn starch; microcrystalline cellulose, e.g. products such as Avicel®, Filtrak®, Heweten® or Pharmacel®; hydroxypropyl cellulose; hydroxyethyl cellulose; hydroxypropylmethyl cellulose, e.g. hydroxypropylmethyl cellulose-Type 2910 USP, hypromellose, and polyvinylpyrrolidone, e.g. Povidone® K30 from BASF. Preferably, hydroxypropylmethyl cellulose-Type 2910 USP is used.

Suitable disintegrants (1.2) according to the invention include but are not restricted to maize starch; CMC-Ca; CMC-Na; microcrystalline cellulose; cross-linked PVP, e.g. as known and commercially available under the trade names Crospovidone®, Polyplasdone®, available commercially from the ISP company, or Kollidon® XL; alginic acid; sodium alginate; and guar gum. Preferably, cross-linked PVP, e.g. Crospovidone® is used.

As glidants (1.3), one or more of the following may be used: silica; colloidal silica, e.g. colloidal silica anhydrous, e.g. Aerosil® 200, magnesium trisilicat, powdered cellulose, starch and talc. Preferably colloidal silica anhydrous or/and colloidal silicon dioxide are used.

As lubricants (1.4) one or more of the following may be used Mg-, Al- or Ca-stearate, PEG 4000 – 8000 and/or talc. Preferably magnesium stearate is used.

One or more of these excipients can be selected and used having regard to the particular desired properties of the tablet by routine experimentation.

According to the present invention, the amount of binder (1.1) may vary within a range of from about 1 to 40%, preferably 1 to 30%, in particular 1 to 25% in weight based on the total weight of the tablet.
The amount of disintegrant (1.2) may vary within a range of from to 5 to 40%, e.g. 10 to 35% in weight based on the total weight of the tablet.
The amount of glidant (1.3) may vary within ranges of from 0.1 to 10%, in particular 0.1 to 5%, e.g. 0.5 to 3% in weight based on the total weight of the tablet or 2 to 4 % in weight based on the total weight of the tablet.
The amount of lubricant (1.4) may vary within a range of from 0.1 to 5%, e.g. 0.5 to 2% in weight based on the total weight of the tablet.

The amount of basic coating (1.5) may vary from 1 to 10 %, preferably from 1.5 to 5 % in weight based on the total weight of the tablet.

It will be appreciated that any given excipient may serve more than one function e.g. as disintegrant, binder, glidant, and/or lubricant.

In a preferred aspect of the invention, the tablet comprises the following excipients, one or more binders in a total amount of about 1% to 25% in weight based on the total weight of the tablet, one or more disintegrants in a total amount of about 10% to 35% in weight based on the total weight of the tablet, one or more glidants in a total amount of about 0.5% to 3% in weight based on the total weight of the tablet, and/or one or more lubricants in a total amount of about 0.5% to 2% in weight based on the total weight of the tablet.

The absolute amounts of each excipient and the amounts relative to other excipients is similarly dependent on the desired properties of the tablet and may also be chosen by routine experimentation. For example, the tablet may be chosen to exhibit accelerated and/or delayed release of Compound I with or without quantitative control of the release of active agent. Preferably the tablet is chosen to exhibit immediate release of the Compound I, e.g. the Compound I monomesylate salt beta crystal form.

The present inventors have encountered difficulties in the production of Compound I tablets due to high friability values and poor abrasion resistance. Further, the flexibility in the quantity of excipients, e.g. disintegrants, is limited due to the high drug load of the product. Thus, there still exists a need for commercially acceptable Compound I dosage forms for oral administration with good patient convenience and acceptance.

In accordance with the present invention, it has now unexpectedly been found that stable and convenient galenic tablets comprising Compound I are obtainable. The present Applicants have found that pharmaceutically acceptable oral solid dosage forms in the form of tablets, being particularly convenient to administer and stable, may be obtained by preparation of tablets by compression methods. More specifically, the tablets of the invention may be prepared by granulation, preferably wet-granulation, followed by compression methods. Compound I, especially the mesylate salt, exhibits high particle size, e.g. 60% of the Compound I starting material having a particle size greater

or equal to 100 μm, e.g. 90% of the particles are smaller or equal to 420 μm. Wet-granulation process is usually performed with a starting material of particle size lower than 100 μm.

It is a characteristic of the tablet according to the invention that it contains a high content of Compound I given the relatively small amount of excipients. This enables the production of physically small tablets. The total amount of excipients in a given unit dosage may be about 70% or less by weight based on the total weight of the tablet, more particularly about 50% or less. Preferably the excipient content is in the range of about 30 to 55%, more particularly 35 to 50% in weight based on the total weight of the tablet.

Tablets according to the invention surprisingly provide for the administration of Compound I in a smaller size than was hitherto possible for a given unit dose of Compound I. The tablets of the invention are, despite the high drug loading, small, and, therefore, convenient to administer. This leads to a better patient compliance.

In another embodiment this invention provides a tablet comprising from 50 mg to 600 mg Compound I, e.g. of from 100 mg to about 400 mg. Most preferably, tablets according to the invention are tablets containing 100 mg and/or tablets containing 400 mg of Compound I.

Accordingly, the present invention provides for tablets containing an amount of Compound I mesylate, e.g. Compound I mesylate alpha crystal form and/or Compound I mesylate beta crystal form, equal to 100 mg and/or 400 mg of Compound I free base. Most preferably, the Compound I mesylate form used for the tablet according to the invention is the beta crystal form.

According to the invention, the process for the preparation of the tablets consists in forming an inner phase, mixing it together with an outer phase, compressing the obtained mixture and optionally coating the tablet.

The inner phase comprises Compound I. Preferably, the inner phase comprises Compound I and one or more excipients, more preferably one or more binders and most preferably the amount of one or more binders in the inner phase is ranging from about 1 to 30%, preferably 1 to 20% and more preferably 1 to 15%. The binders of the inner phase according to the invention are preferably microcrystalline cellulose and hydroxypropylmethyl cellulose. The amount of microcrystalline cellulose in the inner phase may vary from about 10 to 29%, in particular 12 to 14% in weight

based on the total weight of the tablet. The amount of hydroxypropylmethyl cellulose in the inner phase may vary from 1 to 5%, preferably 1 to 2% in weight based on the total weight of the tablet. The Compound I and the pharmaceutically acceptable excipients of the inner phase are mixed together with water and the mixture is processed for granulation, e.g. using a wet high-shear granulator to form the wet-granulates. The wet-granulates may be then, dried, e.g. using a fluid bed dryer.

The present invention pertains to a process for the preparation of tablets comprising an outer phase. The outer phase consists in a mixture of the inner phase with one or more excipients. The inner phase and one or more excipients of the outer phase are mixed together using, e.g. a diffusion mixer. Preferably, one or more binders are added. Most preferably cellulose microcrystalline is added. Even more preferably, microcrystalline cellulose is added in the range of 1 to 10% in weight based on the total weight of the tablet. In a preferred embodiment of the invention, in the outer phase, the amount of microcrystalline cellulose is around 5% in weight based on the total weight of the tablet. The outer phase according to the invention may also contain one or more disintegrants, most preferably Crospovidone®. In a preferred embodiment, the amount of disintegrant in the outer phase is ranging from about 10 to 30%, preferably 12 to 25%, most preferably about 15%.

In a particular aspect of the invention, one or more glidants are incorporated into the outer phase.

According to the invention, one or more lubricants are incorporated into the outer phase.

In a further aspect of the invention, tablets are performed by compression of the mixture of the inner and the outer phases using, e.g. a tablet press.

Optionally, the tablets may be coated, preferably as described herein after.

In one embodiment of the invention, the process for the preparation of a tablet which comprises

(a) forming an inner phase comprising

(i) mixing the Compound I together with pharmaceutically acceptable excipients

(ii) wet-granulating

(b) forming an outer phase comprising

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(iii) adding further pharmaceutically acceptable excipients to the inner phase and mixing;

(c) forming the tablet by

(iv) compressing the mixture obtained in step (iii) and, optionally

(d) coating.

More specifically, in one aspect the present invention provides a process comprising:

(i) mixing the Compound I and pharmaceutically acceptable excipients, e.g. one or more binders, e.g. microcrystalline cellulose, in a high shear mixer;

(ii) adding water, subjecting the mixture to wetting/kneading, e.g. in a high shear mixer, screening using a screening mill with a rotating impeller, and drying, e.g. in a fluidized bed dryer;

(iii) adding pharmaceutically acceptable excipients, e.g. sieved excipients, such as one or more disintegrants, e.g. Crospovidone®, one or more binders, e.g. microcristalline cellulose, one or more glidant, e.g. colloidal silicon dioxide, and mixing, e.g. in a diffusion mixer;

(iv) adding pharmaceutically acceptable excipients such as one or more lubricant e.g. magnesium stearate, sieving, e.g. hand-sieving, e.g. at 900 μm, and mixing, e.g. in a diffusion mixer;

(v) tabletting the mixture obtained in step (iv) by compression, e.g. in a conventional tablet press, e.g. in an EK-0 Korsch eccentric tabletting machine or a rotary tabletting machine, preferably a rotary machine and

(vi) coating, e.g. in a pan coater, e.g. Glatt, Accela.

By "core" is meant the granulate phase (steps (i) and (ii)) including the active drug Compound I and the outer phase consisting of the excipients.

By "total weight of the tablet" is meant the weight of a tablet being the inner and the outer phases and the coating (if any).

According to the invention, the coating process may be performed at low temperature, e.g. between 30 and 40°C, preferably between 32 and 39°C, most preferably at a temperature ranging from around 35 to around 38°C. The coating process may be performed with a spray rate preferably in the range of 30 to 105 g of coating dispersion per kg of cores per hour, preferably of 35 to 105 g. It has surprisingly been found that swelling of the disintegrants, e.g. Crospovidone®,

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nor sticking of the cores occurred during spraying of the coating mixture, as it would be expected by the person skilled in the art by processing at low temperatures.

Moreover, the tablets exhibit improved abrasion resistance. The physical and chemical stability may be tested in conventional manner, e.g. the tablets may be tested as such by measurement of dissolution, friability, disintegration time, assay for Compound I degradation products, appearance and/or microscopy, e.g. after storage at room temperature, i.e. 25°C, and/or storage at 40°C.

The tablet cores may vary in shape and be, for example, round, oval, oblong, cylindrical or any other suitable shape. A characteristic of tablets according to the invention is their small size having regard to the amount of Compound I or Compound I salt contained therein.

In a preferred embodiment of the invention tablets obtained by the compression method described above are round or oval. The edges of the tablets may be beveled or rounded. Most preferably, the tablets are ovaloid and/or round. The tablets according to the invention may be scored. The ovaloid tablet may be small in dimension e.g. 10 to 20 mm in length, preferably 15 to 20 mm, most preferably 17 to 19 mm; 5 to 10 mm in width, preferably 6.5 to 8 mm. The thickness of the tablet is from 4 to 8 mm, preferably 6 to 8 mm. Compression forces of between 10 to 20 kN are used to prepare the compressed tablet, preferably, 12 to 18 kN. Preferably, the ovaloid tablet contains 400 mg of Compound I. The round tablet may be of the following dimensions, e.g. 5 to 15 mm in diameter, preferably 7 to 10 mm, most preferably about 9 mm. The thickness of the tablet may be from 2 to 5 mm, preferably 2.5 to 4 mm. Compression forces of between 6 to 18 kN are used to prepare the compressed tablet, preferably, 8 to 14 kN. Preferably, the round tablet contains 100 mg of Compound I. Preferably the 100 mg tablet is a scored tablet, most preferably the tablet has a break score on one side.

The tablets of the invention comprising about 100 mg of Compound I may furthermore have a hardness of from about 30 to 140 N, e.g. 40 to 140 N, 30 to 100 N, 40 to 100 N, preferably 50 to 80 N. The tablets of the invention comprising about 400 mg of Compound I may have a hardness of 100 to 270 N, e.g. 100 to 250 N, 160 to 270 N, 160 to 250 N, preferably 195 to 235 N.

The disintegration time of the tablet may be of about 20 min or less. Preferably, for the 100 mg Compound I tablet, the disintegration time is ranging from about 2 to 10 min, preferably 4 to 10

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min, e.g. 4 to 8 min. For the 400 mg Compound I tablet, the disintegration time is, preferably ranging from about 7 to 15 min, preferably 8 to 15 min, e.g. 8 to 14 min.

The friability of the tablets is measured according to the US Pharmacopeia. The friability of the tablets according to the invention monitored following the recommendation of the US Phramacopeia is 0 %.

The tablets of the invention may furthermore be colored and/or the tablets or coating marked so as to impart 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 tablets. Dyes suitable for use in pharmacy typically include carotinoids, iron oxides or chlorophyll. The tablets of the invention may be marked using an imprint code.

Procedures which may be used may be conventional or known in the art or based on such procedures e.g those described in L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 3rd Ed, 1986, H. Sucker et al, Pharmazeutische Technologie, Thieme, 1991, Hagers Handbuch der pharmazeutischen Praxis, 4th Ed. (Springer Verlag, 1971) and Remington's Pharmaceutical Sciences, 13th Ed., (Mack Publ., Co., 1970) or later editions.

The tablets of the invention are useful for human indication of Compound I, e.g. anti-tumor treatment, as indicated by standard tests. The activity and characteristics of the tablets of the invention may be indicated in standard clinical trials and/or animal trials.

The tablets of the invention are particularly useful for, e.g. treatment of non-malignant and malignant proliferative disorders, e.g. leukemias, gliomas, sarcomas, prostate-, breast-, gastro-intestinal-, lung-, ovary tumors.

The tablets of the invention comprising a pharmacologically effective amount of Compound I or Compound I salt may be administered as the sole active drug or with another active drug may be envisaged, e.g. together with simultaneous or separate administration of other drugs.

Furthermore, the tablets of the invention obtained are stable both to the production process and during storage, e.g. for 2 years or even 3 years in conventional packaging, e.g. sealed aluminium

blister packs. Less than about 5%, e.g. 2 or 3% or less of Compound I or Compound I salt may degrade during this time as determined in conventional tests.

The tablets of the invention, e.g. the 100 and 400 mg tablets, are bioequivalent with the marketed hard gelatine capsules (100 mg) of Compound I. The administration of 400 mg of Compound I in hard gelatine capsules (4 x 100 mg) in the form of a single film coated tablet is well tolerated.

Depending on age, individual condition, mode of administration, and the clinical picture in question, effective doses, for example daily dosing of tablets of the invention comprising, e.g. 100-1000 mg, e.g. 100 to 800 mg, preferably 100 to 600 mg, especially 400 mg of Compound I, are administered to patients of about 70 kg bodyweight.

The invention relates also to a method for administering to a human subject in need of such a treatment, Compound I or a pharmaceutically acceptable salt thereof in the form of a tablet, once daily for a period exceeding 3 months. The invention relates especially to such method wherein a daily dose of 100 to 1000 mg, preferably 100 to 800 mg, especially 200 to 600 mg, preferably 400 mg, of Compound I is administered to an adult. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the age, the body weight, general health, drug combination with one or more active drugs, type and severity of the disease.

Accordingly in a further aspect the present invention provides a method of treating a subject which comprises administering a tablet according to the invention comprising a pharmacologically effective amount of Compound I salt to a subject in need of such a treatment, optionally with the simultaneous, sequential or separate administration of another drug e.g. a cyclosporin, a rapamycin, an ascomycin, corticosteroids, cyclophosphamide, azathioprine, methotrexate, brequinar, leflunomide, mizoribine, mycophenolic acid and/or mycophenolate mofetil.

When the tablets of the invention are co-administered within a combined therapy the dosages of the Compound I mesylate may be reduced e.g. to one-half to one-third their dosages when used alone.

The medicament package comprises tablets according to the invention and printed instructions directing that one or more tablets of Compound I be administered orally.

Following non-limitative examples illustrate the invention.

Example 1: Tablet Formulation (100 mg tablet)

Composition per dosage form unit and quantity per batch

Component		Composition per unit (mg)		Quantity per batch (kg)	
Compound I mesylate [1]		[2] 119.500		167.300	
Microcrystalline cellulose [1]	(1.1)	25.000		35.000	
Hypromellose / Hydroxypropyl methylcellulose [1]	(1.1)	2.500		3.500	
Microcrystalline cellulose	[3](1.1)	9.850		13.790	
Crospovidone	(1.2)	28.000		39.200	
Silica, colloidal anhydrous/ Colloidal silicon dioxide	(1.3)	1.250		1.750	
Magnesium stearate	(1.4)	1.400		1.960	
Basic coating premix yellow	(1.5)	7.125	8.550[4]	9.975	14.364[4]
Basic coating premix red	(1.5)	0.375	0.450[4]	0.525	0.756[4]
Total weight		**195.000**	**196.500**	**273.000**	**≈ 275.000**
Units/batch				**1'400'000**	

[1] Components of the granulate, [2] 119.5 mg Compound I mesylate equals 100 mg Compound I free base, [3] Microcrystalline cellulose is added in the outer phase as a dry binder, [4] a 20% manufacturing overage of the coating dispersion is included to cover spray losses during the coating process step.

Tablets of 100 mg of Compound I free base according to the invention and of the above tablet were prepared by wet granulation of a mixture of Compound I salt with (1.1), mixing with [3](1.1), (1.2), (1.3) and (1.4), compressing and coating the resultant tablets with an aqueous dispersion of the coating mixture (1.5).

The coating process may be performed at low temperature, e.g. ranging from around 35 to around 38°C. The coating process may be performed with a spray rate preferably in the range of 30 to 105 g of coating dispersion per kg of cores ("core" corresponds to the compressed inner and outer phase) per hour, e.g. 35 to 105 g per kg of cores per h.

Example 2: Tablet Formulation (400 mg tablet)

Tablets of 400 mg of Compound I according to the invention and of the following tablet were prepared by wet granulation of a mixture of Compound I salt with (1.1), mixing with [3](1.1), (1.2), (1.3) and (1.4), compressing and coating the resultant tablets with an aqueous dispersion of the coating mixture (1.5).

Composition per dosage form unit and quantity per batch

Component		Composition per unit (mg)		Quantity per batch (kg)	
Compound I mesylate [1]		[2]478.000		167.300	
Microcrystalline cellulose [1]	(1.1)	100.000		35.000	
Hypromellose / Hydroxypropyl methylcellulose [1]	(1.1)	10.000		3.500	
Microcrystalline cellulose	[3](1.1)	39.400		13.790	
Crospovidone	(1.2)	112.000		39.200	
Silica, colloidal anhydrous / Colloidal silicon dioxide	(1.3)	5.000		1.750	
Magnesium stearate	(1.4)	5.600		1.960	
Basic coating premix yellow	(1.5)	17.100	20.425[4]	5.985	8.588[4]
Basic coating premix red	(1.5)	0.900	1.075[4]	0.315	0.452[4]
Total weight		**768.000**	**771.500**	**268.800**	**≈270. 000**
Units/batch					**350'000**

[1] Components of the granulate, [2] 478 mg Compound I mesylate equals 400 mg Compound I free base, [3] Microcrystalline cellulose is added in the outer phase as a dry binder, [4] a 20% manufacturing overage of the coating dispersion is included to cover spray losses during the coating process step.

The coating process may be performed at low temperature, e.g. ranging from around 35 to around 38°C. The coating process may be performed with a spray rate preferably in the range of 30 to 105 g of coating dispersion per kg of cores ("core" corresponds to the compressed inner and outer phase) per hour, e.g. 35 to 105 g per kg of cores per h.

Example 3: Dimensions of the tablets

Compound I free base/tablet	Shape and Dimensions
100 mg	Round, 9.1-9.3 mm diameter, curved, bevelled edges, thickness: 2.8-3.4 mm break score on one side
400 mg	Ovaloid, 18.1-18.3 x 7.2-7.4 mm, curved, bevelled edges, thickness: 6.6-7.2 mm

Compound I free base/tablet	Shape and Dimensions
100 mg	Round, 9.1-9.4 mm diameter, curved, bevelled edges, thickness: 2.8-3.4 mm break score on one side
400 mg	Ovaloid, 18.1-18.4 x 7.2-7.5 mm, curved, bevelled edges, thickness: 6.6-7.2 mm

CLAIMS:

1. A tablet comprising a pharmacologically effective amount of Compound I or a pharmaceutically acceptable salt thereof in an amount from about 30% to 80% in weight of the active moiety based on the total weight of the tablet.

2. A tablet comprising

(a) a pharmacologically effective amount of Compound I, and

(b) one or more pharmaceutically acceptable excipients suitable for the preparation of tablets

wherein the Compound I or a pharmaceutically acceptable salt thereof is present in an amount from about 30% to 80% in weight of the active moiety based on the total weight of the tablet.

3. A tablet according to claim 1 or 2 wherein Compound I or a pharmaceutically acceptable salt thereof is present in an amount from about 50% to 80% in weight of the active moiety based on the total weight of the tablet.

4. A tablet according to any one of claims 1 to 3 wherein Compound I is in the monomesylate salt form.

5. A tablet according to claim 4 wherein Compound I monomesylate is in the beta crystal form thereof.

6. A tablet according to any one of claims 1 to 5 wherein the excipient comprises at least one binder.

7. A tablet according to any one of claims 1 to 6 wherein the excipients comprise:

at least one binder in a total amount of about 1% to 25% in weight based on the total weight of the tablet,

at least one disintegrant in a total amount of about 10% to 35% in weight based on the total weight of the tablet

at least one glidant in a total amount of about 0.5% to 3% in weight based on the total weight of the tablet, and/or

at least one lubricant in a total amount of about 0.5% to 2% in weight based on the total weight of the tablet.

8. A tablet according to claim 6 or 7 wherein the binder comprises microcrystalline cellulose or hydroxypropylmethyl cellulose or a mixture thereof.

9. A tablet according to claim 7 or 8 wherein the disintegrant comprises cross-linked polyvinylpyrrolidinone.

10. A tablet according to any one of claims 7 to 9 wherein the glidant comprises colloidal silicon dioxide and/or colloidal anhydrous silica.

11. A tablet according to any one of claims 7 to 10 wherein the lubricant comprises magnesium stearate.

12. A process for the preparation of a tablet according to any one of the preceding claims, which process comprises

(i) mixing the Compound I or pharmaceutically acceptable salts thereof and pharmaceutically acceptable excipients;

(ii) wet-granulating;

(iii) mixing with pharmaceutically acceptable excipients to form a mixture; and

(iv) compressing the mixture obtained in step (iii) to form a tablet.

13. The process according to claim 12 wherein the tablet is coated.

14. A tablet according to any one of claims 1 to 11 prepared by a wet-granulation process.