(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 December 2005 (22.12.2005)

PCT

(10) International Publication Number
WO 2005/120463 A1

(51) International Patent Classification[7]: A61K 9/20, 31/519

(21) International Application Number: PCT/IB2005/051854

(22) International Filing Date: 7 June 2005 (07.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1084/DEL/2004 9 June 2004 (09.06.2004) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RAPIDLY DISINTEGRATING TABLETS OF RISPERIDONE

(57) Abstract: The present invention relates to rapidly disintegrating solid dosage forms of risperidone for oral administration prepared by conventional tabletting procedures. The fast disintegrating tablet contains risperidone, a sugar alcohol, a disintegrant such as a cross-linked carboxymethylcellulose, a metal carbonate.

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Description

RAPIDLY DISINTEGRATING TABLETS OF RISPERIDONE

Technical Field

[1] The present invention relates to rapidly disintegrating tablets of risperidone for oral administration prepared by conventional tableting procedures.

Background Art

[2] Oral intake, particularly in the form of tablets, is generally an effective way of administering drugs. But many patients have difficulty in swallowing conventional tablets and hard gelatin capsules, and consequently do not take medications as prescribed. This is particularly true for pediatric and geriatric patients and patients who are bed-ridden. This also holds for groups of patients where swallowing can initiate a nauseating reaction, for example, patients with gastrointestinal disorders, migraine, etc. This results in a high incidence of non-compliance and ineffective therapy.

[3] Rapidly disintegrating tablets, which disintegrate in the oral cavity with or without the aid of any liquid, are advantageous over conventional tablets, capsules or extemporary suspensions, and thus are commonly used to enhance patient compliance. Rapidly disintegrating tablets also offer the convenience of a readily administered dosage form which can be taken anywhere, anytime, and possibly without water.

[4] Risperidone is one of a new generation of 'atypical' antipsychotic drugs and offer distinct advantages over older agents, including decreased side effects and improved efficacy in treatment of the negative symptoms of psychosis. Risperidone is used to treat psychotic disorders and symptoms such as hallucinations, delusions, and hostility and has good activity against various symptoms and signs associated with schizophrenia. It is primarily indicated for acute and chronic schizophrenic psychoses and other psychotic conditions with positive and negative symptoms. It is also indicated for affective symptoms associated with schizophrenia. It is also found to be efficacious in the therapy of acute bipolar affective disorder.

[5] Risperidone is manufactured by Janssen-Cilag and sold under the brand name Risperdal™. U.S. Patent No. 4,804,663 discloses risperidone and processes for its preparation as well as that of its intermediates. It also discloses a film-coated tablet formulation of risperidone comprising a core having a coating, and other formulations such as capsules, oral solution, oral drops, injectable solution and suppositories. There is no mention, however, of rapidly disintegrating tablet formulations of risperidone.

[6] Different technologies have been developed for obtaining formulations that disintegrate quickly in the oral cavity. Such technologies are available from manufacturers like Cima Labs, Fuisz Technologies Ltd., Prographarm, Yamanouchi-Shaklee and Cardinal Health.

[7] Zydis™ of Cardinal Health, is a freeze dried tablet in which the drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. Janssen Pharmaceutica discloses a technology of preparing a solid dosage form that has a porous network of matrix composition that disperses rapidly in water. The disclosed dosage form is prepared by subjecting a matrix material solution to either lyophilization or solid-state dissolution.

[8] Lyophilization, or freeze-drying, is an expensive industrial process and incurs high capital cost, complex sophistication of equipment, increased handling and processing time and difficulty in packaging. Solid-state dissolution, on the other hand, imposes limitations on the solvents that can be used because the solidification temperature of the first and the second solvent is a critical factor of consideration. Such limitations confer complexities to such process.

[9] The other technologies which are available include Cima Labs' OraSolv™, which is an effervescent direct compression tablet having an oral dissolution time of five to thirty seconds, and DuraSolv™, which is a direct compression tablet having a taste-masked active agent in the form of coated microparticles. PCT application WO 98/46215 filed by Cima Labs, describes a hard, compressed, fast melt formulation having an active ingredient and a matrix of at least a non-direct compression filler and relatively high amount of lubricant.

[10] Fuisz Technologies markets Flash Dose™ which is a direct compression tablet containing a processed excipient called shearform.

[11] U.S. Patent No. 5,464,632 assigned to Prographarm discloses a multiparticulate tablet with high disintegration rate in which the active substance is in the form of coated or non-coated microcrystals or microgranules and wherein the excipients or vehicles, comprise generally a disintegrating agent, a swelling agent and a direct compression soluble diluent.

[12] Yamanouchi markets Wowtab™ which is a buccal disintegrating tablet obtained by granulation of a saccharide of low moldability with a saccharide of high moldability and then compression molding of the granulation product. Yamanouchi also is the assignee of U.S. application no. 2003/0099701, which describes a quick-disintegrating tablet comprising a drug, a diluent, and a saccharide with a relatively lower melting point than the drug and the diluent. A bridge is formed between the drug and/or the diluent particles by melting and then solidification of the saccharide with a low melting point.

[13] The references described above disclose direct compression or granulation for preparing rapidly disintegrating tablets. The direction compression and granulation, however, is disclosed as occurring after some additional or alternative processing steps instead of merely a simple direct compression or granulation.

[14] PCT application WO 99/44580 describes methods for obtaining tablets by the direct compression of mixtures that contain at least one inorganic excipient that is insoluble in water, for example, calcium phosphate, one or more disintegrants, for example, crospovidone and optionally, water soluble excipients. The technology is trademarked as Ziplets™ by Eurand. However, the compositions used contain a high percentage of insoluble excipients, which may leave a high amount of residue in the mouth and give a feeling of grittiness.

[15] PCT application WO 03/103629 by Vita Laboratorios discloses method for preparing orally disintegrating tablets which disintegrate in the mouth in less than 30 seconds. These tablets use a diluent of high dissolution rate and high compressibility, and limit the proportion and size of the particles of the insoluble ingredients. The amount and the particle size of the insoluble ingredients are stressed to be critical for compressibility.

[16] PCT application WO 00/57857 by Yuhan Corporation discloses orally disintegrating tablets that disintegrate in the oral cavity leaving no unpleasant water-insoluble residues and has sufficient hardness. The tablets contain spray-dried mannitol, crospovidone and other excipients, and are formed by direct compression.

[17] U.S. application 2003/069213 discloses a method purported to improve the ability to take by oral administration a preparation containing a drug having an unpleasant taste. The formulation is disclosed as including a sugar alcohol having a heat of dissolution of -20 cal/g or less and a pH adjusting agent.

[18] None of the above cited references appear to disclose rapidly disintegrating composition of risperidone.

[19] We have now discovered that taste-masked, rapidly disintegrating solid oral dosage forms of risperidone can be prepared by conventional tableting procedure using conventional excipients.

Disclosure

[20] Summary of the Invention

[21] In one general aspect there is provided a rapidly disintegrating tablet of risperidone that includes a therapeutically effective amount of risperidone, a sugar alcohol, a disintegrant, a metal carbonate and one or more of pharmaceutically acceptable excipients selected from binder, lubricant, glidant, sweeteners, flavors and coloring agents.

[22] Embodiments of the tablet may include one or more of the following features. For example, the sugar alcohol may be one or more of xylitol, erythritol, sorbitol and mannitol. The binder may be one or more of starch, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxyvinyl polymers and acrylates. The lubricant may be one or more of talc, magnesium stearate, zinc stearate, calcium stearate, sodium stearyl fumarate and stearic acid. The glidant may be one or

more of talc and colloidal silicon dioxide. The sweetener may be one or more of aspartame and saccharine sodium.

[23] The disintegrant may be one or more of cross-linked carboxymethylcellulose sodium, cross-linked polyvinylpyrrolidone, sodium starch glycolate, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, low-substituted hydroxypropyl cellulose and sodium alginate. The disintegrant may be present in an amount ranging from 1% to 15% w/w of the tablet.

[24] The metal carbonate may be one or more of sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate, sodium bicarbonate and potassium bicarbonate. The metal carbonate may be present in an amount ranging from 1 % to 30 % w/w of the tablet.

[25] In another general aspect there is provided a rapidly disintegrating tablet of risperidone that includes a therapeutically effective amount of risperidone, mannitol, cross-linked carboxymethylcellulose sodium and magnesium carbonate. Embodiments of the tablet may include one or more of the features described above.

[26] In another general aspect there is provided a process for the preparation of a rapidly disintegrating tablet of risperidone. The process includes: forming a mix by mixing a therapeutically effective amount of risperidone, a sugar alcohol, a metal carbonate and one or more of pharmaceutically acceptable excipients selected from disintegrant, binder, lubricant, glidant, sweeteners, flavors and coloring agents; and processing the mix into a tablet by conventional tableting procedures.

[27] Embodiments of the process may include one or more of the following features or those described above. For example, the tableting procedure may include direct compression. The tableting procedure may include dry granulation. The dry granulation may be carried out by roller compaction. The dry granulation may be carried out by slugging. The tableting procedure may include wet granulation.

[28] In another general aspect there is provided a process for the preparation of a rapidly disintegrating tablet of risperidone. The process includes: forming a mixture by blending risperidone, mannitol, cross-linked carboxymethylcellulose sodium, magnesium carbonate and one or more of pharmaceutically acceptable excipients selected from binder, lubricant, glidant, sweetener, flavor and coloring agent; and compressing the mixture into a tablet. Embodiments of the process may include one or more of the features described above.

[29] In another general aspect there is provided a method for the treatment of schizophrenia. The method includes administering to a patient suffering from schizophrenia, a rapidly disintegrating tablet that includes a therapeutically effective amount of risperidone, one or more sugar alcohols, one or more disintegrants, and one or more metal carbonates.

[30] Embodiments of the method may include one or more of the following features or those described above. For example, the sugar alcohol may be mannitol, the disintegrant may be cross-linked carboxymethylcellulose sodium, and the metal carbonate may be magnesium carbonate.

[31] In another aspect, there is provided a process for preparing rapidly disintegrating tablet of risperidone wherein the process comprises:

[32] a. blending risperidone, a sugar alcohol, a disintegrant and a metal carbonate;

[33] b. compacting or slugging the blend of step (a);

[34] c. sizing the compacts or slugs of step (b) to form granules;

[35] d. mixing the granules obtained in step (c) with one or more of pharmaceutically acceptable excipients like sugar alcohol, disintegrant, binder, lubricant, glidant, sweeteners, flavors and coloring agents; and

[36] e. compressing the mixture obtained in step (d) into a tablet using appropriate tooling.

[37] Embodiments of the process may include one or more of the features described above.

[38] In another aspect, there is provided a process for preparing rapidly disintegrating tablet of risperidone wherein the process comprises:

[39] a. blending risperidone, a sugar alcohol, a disintegrant and a metal carbonate;

[40] b. granulating blend of step (a) with a granulating liquid;

[41] c. drying and mixing the granules obtained in step (b) with one or more of pharmaceutically acceptable excipients like sugar alcohol, disintegrant, binder, lubricant, glidant, sweeteners, flavors, coloring agents and the like; and

[42] d. compressing the mixture obtained in step (c) into a tablet using appropriate tooling.

[43] Embodiments of the process may include one or more of the features described above.

[44] The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

[45] Detailed Description of the Invention

[46] The terms 'rapid disintegrating tablet' and 'rapidly disintegrating tablet' as used herein are intended to describe tablets which disintegrate when placed in the oral cavity or in water in less than a minute.

[47] The term 'therapeutically effective amount' as used herein is intended to mean from about 0.1 mg to 20 mg of risperidone per tablet, particularly from about 0.1 mg to about 10 mg of risperidone per tablet. Risperidone in the dosage form as described herein may be in a coated or uncoated form.

[48] Risperidone as a drug is unpalatable because of its bitter taste. One theory for the cause of the bitter taste is that the taste sensation of a drug begins when ions or polar molecules of the drug taken into the mouth stimulate the cells of the taste buds. Retarding the ionization of drug molecules will lead to the decrease in solubility of the drug in the oral cavity and keeping it in a non-ionized, insoluble form would impart a taste-masking effect. This forms the basis for including one or more metal carbonates in the formulation. The metal carbonate can be an alkali metal carbonate, such as sodium carbonate and/or potassium carbonate; an alkaline earth metal carbonate such as magnesium carbonate and/or calcium carbonate; and bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like. A particularly suitable metal carbonate is magnesium carbonate. The metal carbonate may be used in an amount ranging from 1% to 30% w/w of the tablet.

[49] In a tableting procedure, the choice of excipients or tableting aids is important to achieving rapid disintegration and suitable physical characteristics like hardness, friability, etc. The excipients include diluent, disintegrant, binder, lubricant, glidant, flavors, sweeteners, coloring agents and the like.

[50] Sugar alcohols that may be used include xylitol, erythritol, sorbitol and mannitol. The s ugar alcohol may be used in a concentration of 25% to 95%, particularly 60% to 90% w/w of the tablet. A particularly suitable sugar alcohol is spray-dried mannitol. Spray dried mannitol is available as Pearlitol™. It is a directly compressible sugar and is nonhygroscopic. It has good dilution capacity due to the size and form of the particle, which makes it possible to accept large amounts of active ingredients that are not easily compressed. It does not add moisture or contribute to moisture pickup. It is also chemically inert. It also has optimum organoleptic properties due to negative dissolution heat and excellent palatability due to its small particle size. These properties make mannitol a useful excipient for tablets because together they protect water-sensitive actives from degradation and do not react with the active ingredient. Further, spray dried mannitol has a particle shape that allows it to be free flowing and easily mixed with other ingredients.

[51] Disintegrants play a major role in the disintegration of tablets. To ensure rapid disintegration in the oral cavity, the choice of a suitable type and optimal amount of disintegrant is important. The disintegrant may be selected from cross-linked carboxymethylcellulose and its sodium salt, cross-linked polyvinylpyrrolidone, sodium starch glycolate, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, low-substituted hydroxypropyl cellulose and sodium alginate. Particularly suitable disintegrants are cross-linked carboxymethylcellulose sodium and cross-linked polyvinylpyrrolidone. When following the granulation process, the disintegrants may be added either intragranulary or extragranularly or both. The con-

centration of the disintegrant may vary from 1% to 15%, particularly from 3% to 10% w/w of the tablet.

[52] Binding agents are generally used in a tablet to impart cohesive properties to the tableted blend. Binders that may be used are selected from the group that includes starch; polyvinylpyrrolidone; hydroxypropyl cellulose; hydroxypropyl methyl-cellulose; carboxyvinyl polymers like carbomers; acrylates like Eudragits; and other such materials routinely used in the art of solid dosage form manufacturing for the purposes of binding and preparation of granules. The binding agent may be present in an amount varying from about 1% to about 10% by weight, and particularly from about 3% to about 8% w/w of the tablet.

[53] The granulating liquid may comprise a solution or dispersion of the binder or may be a pharmaceutically acceptable liquid like water, ethanol, etc. when the binder is premixed with the blend to be granulated.

[54] Lubricants may be selected from the group that includes talc, magnesium stearate, zinc stearate, calcium stearate, sodium stearyl fumarate and stearic acid. Glidants may be selected from talc, colloidal silicon dioxide, and the like. The lubricants and glidants may be used in a concentration varying from 0.5% to 5% w/w of the tablet. It should be appreciated that a person skilled in the art is cognizant of the fact that certain excipients can be used both as a lubricant and a glidant.

[55] Sweeteners may be selected from the group that includes aspartame, saccharine sodium, sucrose, dextrose, fructose, sorbitol and the like.

[56] The tablets may also include flavorants and coloring agents. Generally any pharmaceutically acceptable flavoring additive can be used such as, for example, menthol. Colors may be selected from the group that includes ferric oxide, titanium dioxide, F.D. & C. and D. & C. dyes and the like.

[57] The tablets as described herein can be prepared by direct compression, compaction or by wet granulation techniques.

[58] The direct compression method may comprise preparing a blend comprising risperidone, sugar alcohol, metal carbonate, disintegrant, binder, lubricants, glidants, sweeteners and flavors. The blend then is compressed into a tablet using appropriate tooling.

[59] Dry granulation may be carried out by slugging or roller compaction with roller compaction being particularly suitable. The roller compactor functions by uniformly applying pressure on a mixed powder blend by passing the blend between two counter-rotating rollers. The pressure imparted on the blend by the roller compresses the powder into a compact, such as a sheet or ribbon, which is milled to produce granules. In one aspect of the process, risperidone and one or more pharmaceutical excipients selected from sugar alcohol, metal carbonate, disintegrant, binder, lubricant or glidant

are blended and transferred to a roller compactor in a known manner. When in contact with the counter rotating rollers of the roller compactor, the compression force imparted on the blend by the rollers converts the powdered form into a ribbon or compaction sheet. The compact sheet is fed to a mill, such as an oscillatory mill filled with a screen. After passing through the mill and the screen, the compact gets converted into granules of desired particle size distribution. The granules may further be mixed with sugar alcohol, binder, disintegrant, lubricant, glidant, sweeteners and flavors prior to compressing into tablets or may be compressed as such.

[60] In wet granulation, risperidone, disintegrant, sugar alcohol, and metal carbonate are granulated with a solution/dispersion of the binder. Alternatively, the binder is added to the above blend and the resulting blend is granulated with a suitable solvent. The granules are dried and may be mixed with other excipients like sugar alcohol, binder, disintegrant, lubricant, glidant, sweeteners and flavors and compressed into tablets using appropriate tooling.

[61] In one embodiment, rapid disintegrating tablets of risperidone may be prepared by blending risperidone, mannitol, a disintegrant and a metal carbonate with binder, lubricant, glidants, sweeteners, flavors and coloring agents; and compressing the mixture into a tablet using appropriate tooling.

[62] In another embodiment, rapid disintegrating tablets of risperidone may be prepared by blending risperidone, mannitol, a disintegrant and a metal carbonate. The blend then is compacted with a roller compactor and the compacts sized to form granules. The granules are mixed with mannitol, disintegrant, binder, lubricants, glidants, sweeteners, flavors and coloring agents. This mixture then is compressed to obtain tablets using appropriate tooling.

[63] In yet another embodiment, rapid disintegrating tablets of risperidone may be prepared according to the following steps:

[64] blending risperidone, mannitol and a metal carbonate;

[65] granulating the blend with a granulating liquid;

[66] drying and mixing the granules with mannitol, disintegrant, binder, lubricant, glidants, sweeteners, flavors and coloring agents; and

[67] compressing the mixture thus obtained into a tablet using appropriate tooling.

[68] The invention described herein is further illustrated by the following examples but these should not be construed as limiting the scope of the invention. Moreover, references herein to an excipient or component of a formulation should be construed as being in either the singular or the plural form. For example, the term 'a disintegrant' should be construed as encompassing a single disintegrant as well as multiple disintegrants.

[69] **EXAMPLE 1**

[70]

S/N	Ingredients	Weight per tablet (in mg)
1.	Risperidone	1 mg
2.	Spray-dried mannitol	76.259
3.	Magnesium carbonate	7.5
4.	Croscarmellose sodium	6
5.	Low-substituted hydroxypropyl cellulose	3.75
6.	Sodium saccharin	0.625
7.	Aspartame	0.563
8.	Flavor mangora	0.1
9.	Flavor peach apricot	0.05
10.	Flavor peppermint	0.35
11.	Flavor aniseed	0.05
12.	Menthol	0.125
13.	Iron oxide red	0.125
14.	Talc	1
15.	Colloidal silicon dioxide	0.05
16.	Magnesium stearate	2
	Total	**100 mg**

[71] Procedure: Risperidone, spray-dried mannitol, magnesium carbonate, menthol and iron oxide red were sifted. Magnesium carbonate was mixed geometrically with risperidone, menthol and iron oxide red and the blend was further mixed with spray-dried mannitol. Croscarmellose sodium, low-substituted hydroxypropyl cellulose, sodium saccharin, aspartame, flavors, talc and colloidal silicon dioxide were sifted and mixed with the blend obtained above. Magnesium stearate was sifted and added to the resultant blend and the lubricated blend was subsequently compressed into tablets using suitable tooling.

[72] **EXAMPLES 2 - 6**

[73]

		2	3	4	5	6
S/N	**Ingredients**	**Weight per tablet (in mg)**				

Intragranular						
1.	Risperidone	4	3	2	1	0.5
2.	Croscarmellose sodium	12	9	6	3	1.5
3.	Spray-dried mannitol	92	69	46	23	11.5
4.	Magnesium carbonate	30	22.5	15	7.5	3.75
Extra granular						
5.	Croscarmellose sodium	12	9	6	3	1.5
6.	Spray-dried mannitol	203	152.25	101.5	50.75	25.375
7.	Aspartame	2.5	1.875	1.25	0.625	0.3125
8.	Saccharin sodium	2.5	1.875	1.25	0.625	0.3125
9.	Talc	4.0	3.0	2.0	1.0	0.5
10.	Colloidal silicon dioxide	2.0	1.50	1.0	0.5	0.25
11.	Low-substituted hydroxypropyl cellulose	20.0	15.0	10.0	5.0	2.5
12.	Magnesium stearate	8.0	6.0	4.0	2.0	1.0
13.	Flavors	q.s.	q.s.	q.s.	q.s.	q.s.
	Total	**400**	**300**	**200**	**100**	**50**

[74] **Procedure:** Risperidone, spray-dried mannitol, croscarmellose sodium and magnesium carbonate were sifted and mixed in a blender. The blend was compacted using roll compactor and the compacted material was passed through a sieve to obtain granules. Aspartame, saccharin sodium, talc, colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, magnesium stearate, flavors and the remaining amount of croscarmellose sodium and spray-dried mannitol were mixed with compacted granules, and subsequently compressed into tablets using suitable flat bevelled tooling.

[75] **EXAMPLES 7 - 11**

[76]

		7	**8**	**9**	**10**	**11**
S/N	**Ingredients**	**Weight (in mg)**				
Intragranular						
1.	Risperidone	4	3	2	1	0.5
2.	Croscarmellose sodium	6.4	4.8	3.2	1.6	0.8
3.	Spray-dried mannitol	80	60	40	20	10

4.	Magnesium carbonate	30	22.5	15	7.5	3.75
Extra granular						
5.	Croscarmellose sodium	6.4	4.8	3.2	1.6	0.8
6.	Spray-dried mannitol	150	112.5	75	37.5	18.75
7.	Aspartame	2.5	1.875	1.25	0.625	0.3125
8.	Saccharin sodium	2.5	1.875	1.25	0.625	0.3125
9.	Talc	4	3	2	1	0.5
10.	Colloidal silicon dioxide	2	1.5	1	0.5	0.25
11.	Low-substituted hydroxypropyl cellulose	20	15	10	5	2.5
12.	Magnesium stearate	3.2	2.4	1.6	0.8	0.4
13.	Sodium stearyl fumarate	6.4	4.8	3.2	1.6	0.8
14.	Flavors	q.s.	q.s.	q.s.	q.s.	q.s.
	Total	**320**	**240**	**160**	**80**	**40**

[77] **Procedure:** Risperidone, spray-dried mannitol, croscarmellose sodium and magnesium carbonate were sifted and mixed in a blender. The blend was compacted using roll compactor and the compacted material was passed through a sieve to obtain granules. Aspartame, saccharin sodium, talc, colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, magnesium stearate, sodium stearyl fumarate, flavors and the remaining amount of croscarmellose sodium and spray-dried mannitol were mixed with compacted granules, and subsequently compressed into tablets using suitable flat bevelled tooling.

[78] **EXAMPLES 12 - 15**

[79]

		12	**13**	**14**	**15**
S/N	**Ingredients**	**Weight (in mg)**			
Intragranular					
1	Risperidone	1.	1	2	4
2	Crospovidone	1.	3	6	12
3	Spray-dried mannitol	1.	23	46	92

4	Magnesium carbonate	1.	1.	15	30
Extragranular					
5	Crospovidone	1.	3	6	12
6	Spray-dried mannitol	1.	1.	1.	203
7	Aspartame	1.	1.	1.	1.
8	Saccharin sodium	1.	1.	1.	1.
9	Talc	1.	1.	1.	1.
10	Colloidal silicon dioxide	1.	1.	1.	1.
11	Low-substituted hydroxypropyl cellulose	1.	1.	1.	1.
12	Magnesium stearate	1.	1.	1.	1.
13	Flavors	q.s	q.s	q.s	q.s
	Total	**50**	**100**	**200**	**400**

[80] **Procedure:** Risperidone, spray-dried mannitol, crospovidone and magnesium carbonate were sifted and mixed in a blender. The blend was compacted using roll compactor and compacted material was passed through a sieve to obtain granules. Aspartame, saccharin sodium, talc, colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, magnesium stearate, flavors and the remaining amount of crospovidone and spray-dried mannitol were mixed with compacted granules, and subsequently compressed into tablets using suitable flat bevelled tooling.

[81] **EXAMPLE 16**

[82]

S/N	Ingredients	Weight per tablet (in mg)
Intragranular		
1.	Risperidone	1.00
2.	Spray-dried mannitol	23.206

3.	Croscarmellose sodium	3.00
4.	Magnesium carbonate	7.50
5.	Iron oxide red	0.044
6.	Magnesium stearate	0.25
Extra granular		
7.	Spray-dried mannitol	51.772
8.	Croscarmellose sodium	3.00
9.	Low-substituted hydroxypropyl cellulose	3.75
10.	Aspartame	0.564
11	Saccharin sodium	0.626
12.	Talc	1.00
13.	Menthol	0.126
14.	Colloidal silicon dioxide	1.00
15.	Iron oxide red	0.062
16.	Magnesium stearate	2.75
17.	Flavors	q.s.
	Total	**100**

[83] **Procedure:** Risperidone, spray-dried mannitol, croscarmellose sodium and magnesium carbonate were sifted and mixed in a blender. Iron oxide red and magnesium sterate were sifted separately and mixed with the blend obtained above; the blend was compacted using roll compactor and the compacted material was passed through a sieve to obtain granules. Menthol, aspartame, saccharin sodium, talc, colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, iron oxide red, flavors and the remaining amount of croscarmellose sodium and spray-dried mannitol were mixed with compacted granules. Magnesium stearate was sifted and added to the resultant blend and the lubricated blend was subsequently compressed into tablets using suitable flat bevelled tooling.

[84] **EXAMPLES 17 - 21**

[85]

		17	**18**	**19**	**20**	**21**
S/N	**Ingredients**	**Weight (in mg)**				
Intragranular						

1.	Risperidone	4	3	2	1	0.5
2.	Eudragit E100/EPO	4	3	2	1	0.5
3.	Spray-dried mannitol	100	75	50	25	12.5
4.	Magnesium carbonate	30	22.5	15	7.5	3.75
5.	Menthol	0.3	0.225	0.15	0.075	0.0375
6	Ferric oxide	0.5	0.25	0.25	0.125	0.0625
7.	Acetone*	q.s.	q.s.	q.s.	q.s.	q.s.
8.	Water*	q.s.	q.s.	q.s.	q.s.	q.s.
Extragranular						
9.	Croscarmellose sodium	24	18	12	6	3.0
10.	Spray-dried mannitol	202.15	151.6	101.0	50.53	25.26
11.	Low Substituted hydroxypropyl cellulose	11.25	7.5	3.75	1.875	0.94
12.	Aspartame	2.25	1.688	1.125	0.562	0281
13	Sodium saccharin	2.5	1.875	1.25	0.625	0.313
14.	Ferric oxide	1.0	0.75	0.5	0.25	0.125
15.	Talc	4	3	2	1	0.5
16.	Silicon dioxide	2	1.5	1	0.5	0.25
17.	Magnesium Stearate	8	6	4	2	1
18.	Flavors	q.s.	q.s.	q.s.	q.s.	q.s.
	Total	**400**	**300**	**200**	**100**	**50**

[86] * Evaporated during drying

[87] **Procedure:** Menthol and Eudragit E 100 were dissolved in a mixture of acetone and water. Risperidone, spray-dried mannitol, magnesium carbonate and ferric oxide were sifted and mixed in a blender. This blend was granulated with Eudragit solution and granules were dried in a fluidized bed drier. The granules were passed through a sieve. Croscarmellose sodium, low-substituted hydroxypropyl cellulose, aspartame, saccharin sodium, talc, silicon dioxide, magnesium stearate, flavors and the remaining amount of ferric oxide and spray-dried mannitol were mixed with granules, and subsequently compressed into tablets using suitable flat bevelled tooling.

[88] **TABLE 1 : Dissolution profile of tablets of Example 16 as compared to reference (Risperdal ™ M-Tablets of 1 mg strength manufactured by Janssen Cilag) in a USP type II dissolution apparatus at 50 rpm in 500 ml of 0.1 N HCl at**

37 ° C

[89]

Time (min)	% Risperidone dissolved	
	Tablets of Example 16	Risperdal M-Tab
0	0	0
3	96	93
6	99	97
10	99	98
15	99	99
20	99	99
30	99	99

[90] While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

Claims

[1] A rapidly disintegrating tablet of risperidone comprising a therapeutically effective amount of risperidone, a sugar alcohol, a disintegrant, a metal carbonate and one or more of pharmaceutically acceptable excipients selected from binder, lubricant, glidant, sweeteners, flavors and coloring agents.

[2] The rapidly disintegrating tablet according to claim 1, wherein the sugar alcohol comprises one or more of xylitol, erythritol, sorbitol and mannitol.

[3] The rapidly disintegrating tablet according to claim 1, wherein the disintegrant comprises one or more of cross-linked carboxymethylcellulose sodium, cross-linked polyvinylpyrrolidone, sodium starch glycolate, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, low-substituted hydroxypropyl cellulose and sodium alginate.

[4] The rapidly disintegrating tablet according to claim 1, wherein the disintegrant is present in an amount ranging from 1 % to 15% w/w of the tablet.

[5] The rapidly disintegrating tablet according to claim 1, wherein the metal carbonate comprises one or more of sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate, sodium bicarbonate and potassium bi-carbonate.

[6] The rapidly disintegrating tablet according to claim 1, wherein the metal carbonate is present in an amount ranging from 1 % to 30 % w/w of the tablet.

[7] The rapidly disintegrating tablet according to claim 1, wherein the binder c omprises one or more of starch, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxyvinyl polymers and acrylates.

[8] The rapidly disintegrating tablet according to claim 1, wherein the lubricant comprises one or more of talc, magnesium stearate, zinc stearate, calcium stearate, sodium stearyl fumarate and stearic acid.

[9] The rapidly disintegrating tablet according to claim 1, wherein the glidant comprises one or more of talc and colloidal silicon dioxide.

[10] The rapidly disintegrating tablet according to claim 1, wherein the sweetener comprises one or more of aspartame and saccharine sodium.

[11] A rapidly disintegrating tablet of risperidone comprising a therapeutically effective amount of risperidone, mannitol, cross-linked carboxymethylcellulose sodium and magnesium carbonate.

[12] A process for the preparation of a rapidly disintegrating tablet of risperidone, the process comprising:

forming a mix by mixing a therapeutically effective amount of risperidone, a sugar alcohol, a metal carbonate and one or more of pharmaceutically

acceptable excipients selected from disintegrant, binder, lubricant, glidant, sweeteners, flavors and coloring agents; and

processing the mix into a tablet by conventional tableting procedures.

[13] The process according to claim 12, wherein the tableting procedure comprises direct compression.

[14] The process according to claim 12, wherein the tableting procedure comprises dry granulation.

[15] The process according to claim 14, wherein the dry granulation is carried out by roller compaction.

[16] The process according to claim 14, wherein the dry granulation is carried out by slugging.

[17] The process according to claim 12, wherein the tableting procedure comprises wet granulation.

[18] A process for the preparation of a rapidly disintegrating tablet of risperidone, the process comprising:

forming a mixture by blending risperidone, mannitol, cross-linked carboxymethylcellulose sodium, magnesium carbonate and one or more of pharmaceutically acceptable excipients selected from binder, lubricant, glidant, sweetener, flavor and coloring agent; and

compressing the mixture into a tablet.

[19] A method for the treatment of schizophrenia, the method comprising administering to a patient suffering from schizophrenia, a rapidly disintegrating tablet comprising a therapeutically effective amount of risperidone, one or more sugar alcohols, one or more disintegrants, and one or more metal carbonates.

[20] The method of claim 19, wherein the sugar alcohol comprises mannitol, the disintegrant comprises cross-linked carboxymethylcellulose sodium, and the metal carbonate comprises magnesium carbonate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/051854

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K31/519

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)
IPC 7 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 practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	US 2003/069213 A1 (II NORITAKA ET AL) 10 April 2003 (2003-04-10) paragraphs [0001], [0002], [0006] - [0010], [0013], [0016], [0023], [0025], [0029], [0031] - [0033], [0069], [0070], [0078] example 2 claims 1-3,7,12,18 the whole document -----	1-20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2005	19. 09. 2005

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/051854

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/57857 A (YUHAN CORPORATION) 5 October 2000 (2000-10-05) cited in the application the whole document page 1, paragraph 1 page 2, paragraphs 3,4 page 3, paragraph 2 page 5, paragraph 4 table 1.1 examples claims -----	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/051854

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/051854

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