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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 February 2011 (24.02.2011)

PCT

(10) International Publication Number
WO 2011/020527 A1

(51) International Patent Classification:
A23G 3/00 (2006.01) *A23L 1/236* (2006.01)
A23K 1/00 (2006.01) *A23P 1/02* (2006.01)
A23L 1/00 (2006.01) *A61K 9/20* (2006.01)
A23L 1/09 (2006.01) *A23G 3/42* (2006.01)

(21) International Application Number:
PCT/EP2010/004224

(22) International Filing Date:
12 July 2010 (12.07.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09010596.6 18 August 2009 (18.08.2009) EP

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2011/020527 A1

(54) Title: PROCESS FOR COMPRESSING ISOMALT

(57) Abstract: The present invention related to an improved method of producing a compressed product containing isomalt having a volume mean diameter preferably not smaller than 250 μm. The method is based upon agglomeration and the volume mean diameter of the agglomerate is reduced to smaller than 210 μm before compressing the product. Chewable tablets of acceptable hardness are obtained.

Process for Compressing Isomalt

Technical field

The present invention relates to the preparation of an isomalt containing composition suitable for tabletting.

Background of the invention

With the present interest in the use of sugar-free and/or low calorie products, tablets for pharmaceutical, confectionery or food applications are mostly made with sugar alcohols, such as xylitol, maltitol, sorbitol, mannitol and erythritol.

The tablet does not only contain the drug or a reagent, it also contains other ingredients which act as fillers, such as lactose or phosphates; lubricating agents, such as talc, stearic acid or paraffin and disintegrating agents, such as carboxymethyl-cellulose or starch. For confectionery purposes the tablets often include aroma's and colorants at low concentration.

US 6,224,904 relates to a compressed formulation containing 1-glucopyranosyl-sorbitol or a mixture of sweetening agents composed of 1-glucopyranosyl-sorbitol, 6-glucopyranosyl-sorbitol and 1-glucopyranosyl-mannitol. A mixture with increased 1-glucopyranosyl-mannitol is used for the production of chewable tablets.

US 6,849,286 relates to a method of producing an improved compressed product wherein the agglomeration of the ingredients is induced. The invention provides that according to a first procedure step the educt, namely isomaltulose, isomalt and/or the mixtures containing 6-glucopyranosyl-sorbitol and 1-glucopyranosyl-mannitol, is milled while dry and the particles should have a maximum size of 100 µm.

There is a further interest for having an improved method for preparing a compressed product containing isomalt and which can be used as an excipient in tablets.

Summary of the invention

The current invention relates to a method of producing a compressed product of a dry isomalt wherein 6-glucopyranosyl-sorbitol is present in a weight percentage from 43% to 57% and 1-glucopyranosyl-mannitol in a weight percentage from 57% to 43%, and said method is comprising the following steps:

a. Agglomerating the isomalt having a volume mean dimater not smaller than 250 µm with a liquid binder,
b. At the same time or thereafter drying of the agglomerate,
c. Reducing volume mean diameter of agglomerate to a volume mean diameter smaller than 180 µm, preferably smaller than 150 µm, more preferably smaller than 110 µm,
d. Compressing the agglomerate with reduced volume mean diameter into a compressed product.

In the current invention the liquid binder is water, liquid sorbitol, maltodextrin and water, and/or mixtures thereof, and the agglomeration is applying a fluidized bed.

Detailed description of the invention

The current invention relates to a method of producing a compressed product of a dry isomalt wherein 6-glucopyranosyl-sorbitol is present in a weight percentage from 43% to 57% and 1-glucopyranosyl-mannitol in a weight percentage from 57% to 43%, and said method is comprising the following steps:

e. Agglomerating the isomalt having a volume mean dimater not smaller than 250 µm with a liquid binder,
f. At the same time or thereafter drying of the agglomerate,
g. Reducing volume mean diameter of agglomerate to a volume mean diameter smaller than 180 µm, preferably smaller than 150 µm, more preferably smaller than 110 µm,
h. Compressing the agglomerate with reduced volume mean diameter into a compressed product.

Isomalt is understood to refer to an almost equimolar mixture of 6-glucopyranosyl-sorbitol (6-GPS) and 1- glucopyranosyl-mannitol (1-GPM), and the weight percentage can vary between 43 to 57% of 6-GPS to 57% to 43% of 1-GPM. The isomalt may further comprise minor amounts of other substances such mannitol, sorbitol, hydrogenated or non-hydrogenated oligosaccharides as well as optionally glucose, fructose and/or sucrose, trehalulose, isomaltulose or isomaltose.

The isomalt used for the agglomeration step has a volume mean diameter not smaller than 250 µm preferably not smaller than 300 µm, more preferably not smaller than 400 µm. Preferably, the volume mean diameter is not bigger than 1000 µm. Even when starting from isomalt with an even smaller volume mean diameter, such as not smaller than 150 µm, the

process still required the step of reducing the volume mean diameter of agglomerate to a volume mean diameter smaller than 110 µm, preferably smaller than 90 µm.
While adding a liquid binder, the product is agglomerated and this agglomerate can be dried during agglomeration or thereafter.

Agglomeration (granulation) methods can be divided in two basic types, namely wet methods, which use a liquid in the process, and dry methods in which no liquid is used. Wet granulation is most often used and involves many steps, including: agglomerating (granulating) of dry primary powder particles of active ingredients and excipients in the presence of a granulating fluid upon agitation using low-shear or high-shear mixers or fluidized beds, wet sieving (wet screening) to remove larger lumps, drying the granulated product, and milling or sieving (screening) the dried granulated product to achieve a granulated product having the desired granule size distribution. The obtained granulated product may subsequently be tabletted.

Surprisingly, it was found that the isomalt having a volume mean diameter of not smaller than 250 µm can directly be agglomerated into an agglomerate. No milling step is required.
In order to obtain about uniform sized particles, the volume mean diameter of the dried agglomerate is reduced to a volume smaller than 210 µm, preferably smaller than 180 µm, more preferably smaller than 150 µm, even more preferably smaller than 110 µm, most preferably smaller than 90 µm. The volume mean diameter is measured by laser technology. Any method is applicable for reducing the volume mean diameter of agglomerate to a volume mean diameter smaller than 210 µm. The granules (agglomerate) formed in step c) of the current process are pressed through a sieve of a predetermined size. Preferably a screening machine, more preferably an oscillating screening machine is applied for this sieving. At the same time or thereafter the product is dried.

Any drier type can be applied for drying of the granules, but preferably a fluid bed is applied for this purpose. These uniform sized particles are compressed to obtain a compressed product in a typical tabletting equipment.

The current invention relates to a method wherein the liquid binder is water, liquid sorbitol, maltodextrin and water, and/or mixtures thereof.
The liquid binder is added in an amount from 2 to 25% based upon the dry matter of isomalt. Whenever the liquid binder is water, it is added in an amount of 2 to 10%, preferably 4 to 8% based upon the dry matter of the isomalt. The liquid binder may also be liquid sorbitol applied in a dry matter concentration of at least 50%, preferably 60%, more preferably at least 70%.

The liquid binder (= total amount of liquid sorbitol) is added in an amount of 2% to 10%, preferably 4 to 7% based upon the dry matter of the isomalt.

Maltodextrin can be added in dry form and water is added during granulation. Alternatively, maltodextrin and water is used as a liquid binder. Maltodextrin is a polysaccharide that is used as a food additive. It is hydrolysate produced from starch and consists of D-glucose units connected in chains of variable length. The glucose units are linked with α(1→4) bonds. Maltodextrin is typically composed of mixtures of chains that vary from three to nineteen glucose units long. Maltodextrins are classified by DE (dextrose equivalent) and have a DE of 20 or lower, mostly between 5 to 20. The total amount of liquid binder (= maltodextrin and water) is from 15 to 25%, preferably from 17% to 23% based upon the dry matter of the isomalt. The liquid binder which is consisting of maltodextrin and water, is containing maltodextrin in an amount of 15% to 20%, preferably about 18% based upon total weight of liquid binder.

In a preferred embodiment, the method according to the current invention is applying a fluidized bed for the agglomeration. The drying can be performed in the fluidized bed as well, when the bed is heated to a temperature above room temperature.

Additives other than isomalt or auxiliary substances such as lubricants are added between the drying and the compressing step and before/after the step of reducing the volume mean diameter. Additives other than isomalt can be added to preserve flavor or enhance taste and appearance. Such substances may include sweeteners, flavorings, taste substances and coloring agents, food-compatible acids, disintegrants, monosaccharides, disaccharides, monosaccharide alcohols, disaccharide alcohols different from isomalt, starch, starch derivatives, pectins, polyvinylpyrrolidone, cellulose, cellulose derivatives, intense sweeteners, stearic acid or the salts thereof, or inulin. Preferably, as a lubricant agent in tablet formation, magnesium stearate, calcium stearate, stearic acid, sucrose fatty acid esters, and/or talc and the like can be added according to needs. Furthermore surface active agents such as sodium lauryl sulfate, propylene glycol, sodium dodecanesulfonate, sodium oleate sulfonate, and sodium laurate mixed with stearates and talc, sodium stearyl fumarate, sucrose fatty acid esters, and the like can be added according to needs. These additives other than isomalt or auxiliary substances may be occasionally added during the agglomeration step as well.

If compressed products (tablets) are prepared for pharmaceutical applications an active ingredient different from isomalt and fillers, lubricating agents or disintegrating agents are added if needed. Such an active ingredient is different form isomalt and may be a substance in a pharmaceutical drug or cosmetics, detergents, fertilizer or agrochemical products that is biologically active. Preferably the active ingredient is added during the agglomeration.

The term "tablet", as used herein, includes any tablet, in particular tablets in any form, shape and of any physical, chemical or sensory property, and tablets for any route of administration, indication and application. The tablet produced according to the invention is a chewable tablet. A chewable tablet according to the present invention is a soft tablet where chewing helps to break the tablet particles and release the active ingredient, flavor, aroma or the like, in the mouth before swallowing. Chewable tablets are designed to be mechanically disintegrated in the mouth. A chewable tablet dosage form can be a soft pill, tablet, gum and more recently "chewy squares". The tablet hardness is a highly important property of a chewable tablet comprising active ingredient(s) and having desirable chewability properties.

The compressed product (tablet) obtained according to the method of the current invention, is showing a hardness of from 120 to 300 N at a compression force of from 10 to 20 kN, preferably a hardness of from 125 to 280 N, more preferably from 130 to 270 N for tablets having a surface of 1 cm^2, a diameter of 11.3 mm and a weight of 350 mg.

Said tablets can be applied in food applications, feed, pharma applications, cosmetics, detergents, fertilizer or agrochemical products. In fact, without being limiting, the compressed product of the current invention can be used in food products, animal feed, health food, dietetic products, animal medicine, with bath agent, in agrochemical products, with fertilizer, with plant granules, with plant seeds or seed grains, and any other product being it ingested by humans and/or animals or any other product which can benefit from the improved properties of the compressed product of the current invention. The compressed product of the current invention can be used as carrier for additives based on enzymes or microorganisms, detergent tablets, vitamins, flavors, perfumes, acids, sweeteners, different from isomalt or various active ingredients with medicinal or non-medicinal applications. Eventually mixtures of additives different from isomalt can be applied.
If tablets are prepared for food (confectionery) applications than in general up to about 99 % (w/w) consists of the isomalt,and aroma, colorants, flavors and a lubricating agent, are added.

The invention will hereunder be illustrated in the form of the following examples.

Examples

Methods for evaluating granule and tablet properties

The granules were characterized by their volume mean diameter (size distribution).
The following measurement method was employed.

Size distribution. Size distribution was determined according to the European Pharmacopoeia VI Test method 2.9.31 using a laser light particle sizer, type Helos KF – Rodos T4.1, of Sympatec GmbH (Germany). The particle size was analysed by laser light diffraction.

The tablets were characterized by their hardness. For each compression force, 10 tablets for hardness were analyzed and mean values were calculated. The following measuring method was employed.

Hardness. Hardness, i.e. the diametral crushing strength, was determined according to the European Pharmacopoeia VI Test method 2.9.8 Resistance to crushing of tablets by using a conventional pharmaceutical hardness tester (hardness tester model Multicheck V, available from Erweka GmbH (Germany)). In order to compare values across different size tablets, the breaking strength was normalized for the area of the break. The normalized value, expressed as N/mm^2, is herein referred to as tensile strength (Ts) and calculated as follows:

$Ts = 2H/\pi TD$,

wherein H is the hardness, T the thickness and D the diameter of the tablet. For each compression force, 10 tablets were analyzed on hardness (H), thickness (T) and diameter (D).

Example 1

The bed of the fluid bed (Aeromatic-Fielder GEA – Strea-1) was filled with 300 g (Cargill C*PharmIsoMaltidex™ new grade 2009, having a volume mean diameter of 386 µm) and 25 g water was sprayed onto the powder at 1 Bar, at 2.8 g/min at a bed temperature of 60°C.

The drying of the granules was done on the same equipment for additionally 60 minutes at 50°C.

The dried granules were screened in the granulator (Erweka (FGS + AR400E) over a sieve of 0.125 mm to 0.250 mm for 10 to 15 minutes at 100 turns per minute. The volume mean diameter of the granules was 78 µm.

The dry sieved granules were then blended with 1% of magnesium stearate in a Pharmatech Equipment at 28 rpm.

Example 2

The granulated product obtained in example 1 was then tabletted in a tabletting machine (Korsch - PH100) at compression forces varying from 5 kN to 30 kN.

Tablets had a surface of 1 cm^2, the diameter of the tablet was 11.3 mm and the weight is 350 mg.

The thus obtained tablets were analyzed as follows:

Hardness comparison

Compression Force (kN)	Product from example 2 (N)
10	130
15	208
20	274

Example 3

Example 1 and 2 were repeated but instead of using isomalt (Cargill C*PharmIsoMaltidex™ new grade 2009) isomalt (C*IsoMaltidex 16506 from Cargill) was applied. The recipe, the procedure as well as the outcome of the experiments was exactly the same as laid out in example 1 and 2.

Claims

1. A method of producing a compressed product of a dry isomalt wherein 6-glucopyranosyl-sorbitol is present in a weight percentage from 43 to 57% and 1-glucopyranosyl-mannitol in a weight percentage from 57% to 43% and said method is comprising the following steps:
   a. Agglomerating the isomalt having a volume mean diameter not smaller than 250 µm with a liquid binder,
   b. At the same time or thereafter drying of the agglomerate,
   c. Reducing volume mean diameter of agglomerate to a volume mean diameter smaller than 180 µm, preferably smaller than 150 µm, more preferably smaller than 110 µm,
   d. Compressing the agglomerate with reduced volume mean diameter into a compressed product.

2. A method according to claim 1 characterized in that liquid binder is water, liquid sorbitol, maltodextrin and water, and/or mixtures thereof.

3. A method according to claim 1 characterized in that the liquid binder is present in an amount of from 2 to 25% based upon the dry matter of isomalt.

4. A method according to anyone of claims 1 to 3 characterized in that the agglomeration is applying a fluidized bed.

5. A method according to anyone of claims 1 to 4 characterized in that active ingredient different from isomalt is added in step a).

6. A method according to anyone of claims 1 to 5 characterized in additives different from isomalt and/or flavors are added between step c) and d).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/004224

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23G3/00 A23K1/00 A23L1/00 A23L1/09 A23L1/236
A23P1/02 A61K9/20 A23G3/42
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)
A23G A23K A23L A23P 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, BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BOLHUIS G K ET AL: "Compaction properties of isomalt" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 72, no. 3, 1 August 2009 (2009-08-01) , pages 621-625, XP026218302 ISSN: 0939-6411 [retrieved on 2009-03-25] paragraph [03.1]; table 1	1-6
X,P	EP 2 095 815 A1 (LESVI S L LAB [ES]) 2 September 2009 (2009-09-02) paragraphs [0052] - [0054]; example 3	1-6
X	US 6 849 286 B1 (BAYERKOEHLER THEODOR [DE] ET AL) 1 February 2005 (2005-02-01) example 1	1-6

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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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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2010	20/10/2010

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/004224

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/020268 A1 (CHOONGWAE PHARMA CORP [KR]; HAN MI-KYOUNG [KR]; CHOI JIN-WOO [KR]; KIM) 12 February 2009 (2009-02-12) tables 1-3, 8, 9	1-6
A	NDINDAYINO F ET AL: "Characterization and evaluation of isomalt performance in direct compression" INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER BV, NL, vol. 189, no. 1, 28 October 1999 (1999-10-28), pages 113-124, XP002486902 ISSN: 0378-5173 paragraph [2.2.2]; tables 1,2	1-6
A	WO 2005/115342 A1 (NYCOMED DANMARK APS [DK]; MATHIESEN JACOB [DK]; NIELSEN CARSTEN MARTIN) 8 December 2005 (2005-12-08) page 34; claims 63,64; figures 11,12	1-6
A	WO 2009/015791 A2 (SUEDZUCKER AG [DE]; HENKEL AG & CO KGAA [DE]; HAUSMANNS STEPHAN [DE];) 5 February 2009 (2009-02-05) examples 1,5	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/004224

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2095815 A1	02-09-2009	US 2009214646 A1	27-08-2009
US 6849286 B1	01-02-2005	AT 283705 T	15-12-2004
		AU 779334 B2	20-01-2005
		AU 7652300 A	17-04-2001
		BR 0013885 A	07-05-2002
		CA 2384422 A1	21-03-2001
		DE 19943491 A1	15-03-2001
		WO 0119401 A1	22-03-2001
		EP 1214093 A1	19-06-2002
		ES 2233453 T3	16-06-2005
		IL 148194 A	31-10-2006
		JP 2003509384 T	11-03-2003
		MX PA02001679 A	23-10-2002
		NZ 518208 A	27-02-2004
		PT 1214093 E	29-04-2005
		RU 2222349 C2	27-01-2004
WO 2009020268 A1	12-02-2009	NONE	
WO 2005115342 A1	08-12-2005	AU 2005247060 A1	08-12-2005
		BR PI0511520 A	26-12-2007
		CA 2581703 A1	08-12-2005
		CN 101001611 A	18-07-2007
		EA 200602175 A1	29-06-2007
		EP 1753403 A1	21-02-2007
		JP 2008500290 T	10-01-2008
		KR 20070043714 A	25-04-2007
		US 2008175904 A1	24-07-2008
		ZA 200609724 A	27-05-2009
WO 2009015791 A2	05-02-2009	EP 2185002 A2	19-05-2010
		US 2009035355 A1	05-02-2009