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CA 2458209 C 2010/11/09

(11)(21) 2 458 209

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2002/08/24
(87) Date publication PCT/PCT Publication Date: 2003/03/13
(45) Date de délivrance/Issue Date: 2010/11/09
(85) Entrée phase nationale/National Entry: 2004/02/20
(86) N° demande PCT/PCT Application No.: EP 2002/009484
(87) N° publication PCT/PCT Publication No.: 2003/020265
(30) Priorité/Priority: 2001/09/03 (EP01121067.1)

(51) Cl.Int./Int.Cl. *A61K 31/375* (2006.01), *A61K 9/16* (2006.01), *A61K 9/20* (2006.01)

(72) Inventeurs/Inventors:
CHEN, CHYI-CHENG, CH;
LEUENBERGER, BRUNO, CH

(73) Propriétaire/Owner:
DSM IP ASSETS B.V., NL

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : COMPOSITIONS CONTENANT UNE PECTINE ET DE L'ACIDE ASCORBIQUE
(54) Title: COMPOSITIONS COMPRISING PECTIN AND ASCORBIC ACID

(57) Abrégé/Abstract:
Ascorbic acid compositions in the form of a powder and/or granules contain as principal components L-ascorbic acid and/or a pharmaceutically acceptable salt thereof, and a high molecular (300 kDalton or higher) pectin. The compositions are compressible into tablets with improved mechanical strength and hardness.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 March 2003 (13.03.2003)

PCT

(10) International Publication Number
WO 03/020265 A3

(51) International Patent Classification[7]: A61K 31/375, 9/16, 9/20

(21) International Application Number: PCT/EP02/09484

(22) International Filing Date: 24 August 2002 (24.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01121067.1 3 September 2001 (03.09.2001) EP

(71) Applicant *(for all designated States except US)*: **ROCHE VITAMINS AG** [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basle (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHEN, Chyi-Cheng** [US/CH]; 18 Lindenstrasse, CH-4102 Binningen (CH). **LEUENBERGER, Bruno** [CH/CH]; Muehlebachweg 23, CH-4123 Allschwil (CH).

(74) Agents: **LEDERER, Franz** et al.; Lederer & Keller, Prinzregentenstrasse 16, D-80538 München (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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

Published:
— *with international search report*

(88) Date of publication of the international search report:
4 September 2003

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.

WO 03/020265 A3

(54) Title: COMPOSITIONS COMPRISING PECTIN AND ASCORBIC ACID

(57) Abstract: Ascorbic acid compositions in the form of a powder and/or granules contain as principal components L-ascorbic acid and/or a pharmaceutically acceptable salt thereof, and a high molecular (300 kDalton or higher) pectin. The compositions are compressible into tablets with improved mechanical strength and hardness.

Compositions comprising pectin and ascorbic acid

The present invention relates to a composition in the form of a powder and/or granules, which contain as principal components L-ascorbic acid and/or a pharmaceutically acceptable salt thereof, and high molecular pectin. The composition according to the present invention is directly compressible into tablets with good taste, improved mechanical strength and hardness, with excellent color stability and is free of sugar and starch. The addition of adjuvants and excipients to the composition for producing tablets is optional.

Compositions comprising L-ascorbic acid and/or a pharmaceutically acceptable salt thereof and pectin, as well as tablets manufactured using such compositions have been described in European Patent Application No.1 110 550 A2.

It has now been found that tablets manufactured using a composition comprising L-ascorbic acid and/or its salts, and high molecular pectin show improved hardness as compared to tablets manufactured using conventional pectin of lower molecular weight.

Thus, in one aspect the invention relates to a composition in the form of a powder or granules comprising:

(a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof,

(b) high molecular pectin and, optionally,

(c) adjuvants and excipients.

The term "high molecular pēctin" as used herein denotes pectin having an average molecular weight of about 300 kDalton or higher. The preferred high molecular pectins are those having an average molecular weight of from about 300 kDalton to about 400 kDalton, particularly 350 kDalton. Such pectins can be obtained as disclosed in US patent specification No. 6,143,337 (inventors: Marshall L. Fishman and Hoa K. Chau, assignors to The United States of America as represented by the Secretary of Agriculture) the contents of which is incorporated herein by reference. The average molecular weight is determined by size exclusion chromatography having a multi angle laser light scattering detector as described in US patent No. 6,143,337. However, pectins of higher molecular weight, e.g. up to 2000 kDalton can be used also in the present invention. Pectins of such molecular weight can be obtained e.g. from Asteraceae plants, especially cichory and Jerusalem artichoke, see International patent application WO 99/03892. Fractions of the desired high molecular weight can be obtained from such pectins by membrane filtration, e.g. using polyethersulfone or composite regenerate cellulose membranes as supplied by Millipore Corporation, Bedford, MA 01730, USA, under the trade name Pellicon® Tangential Flow Filtration Cassettes.

In accordance with the present invention, the high molecular pectin is preferably used in quantities within the range of about 0.1% to about 10% by weight, preferably in quantities of about 0.5% to about 5% by weight and most preferably in quantities of about 0.5% to about 2% by weight, calculated to the total weight of the composition thereof. Experiments have shown that a composition consisting of 95-99% by weight of L-ascorbic acid and/or the pharmaceutically acceptable salt thereof and 5-1% by weight of pectin, the two components totalling 100% by weight, i.e. with no other components present, yield tablets of very good quality and excellent color stability.

Adjuvants may optionally be added. Suitable adjuvants are for example starch, HPMC, polyols. Preferably no adjuvants are added.

The composition of this invention may be produced by any method known *per se* for the production of powders or granules. Preferred are fluidized-bed granulation, high-shear granulation, extrusion, spray-drying and wet granulation.

For obtaining the composition of the present invention by spray-drying it is convenient to prepare an aqueous slurry of all the components. The slurry has preferably a solid content of about 10 to 70% by weight, and preferably about 30 to 70% by weight. The slurry is then spray-dried in a manner known per se.

For obtaining the composition of the present invention by fluidized-bed granulation it is convenient to use a known fluidized-bed granulating apparatus which comprises a fluidized-bed drying device fitted with spray means. Preferably the L-ascorbic acid and/or a pharmaceutically acceptable salt thereof form the fluidized bed, which is fluidized by air or an inert gas, e.g. nitrogen. The pectin, as well as optional adjuvants, dissolved in an appropriate amount of water and sprayed in the form of an atomized mist onto the fluidized particles in such a manner that the granulating and drying operations is accomplished in a single step. The granulating process is continued until the desired amount of the pectin binder has been deposited onto the fluidized particles. The granules are sieved to remove the fractions of granules which are either too large or too small. Preferably, the particle size of the granules is within 100 and 1000 micron, more preferably between 125 and 850 microns. While the so-obtained granules are substantially dry they may contain a very small percentage of water depending on the amount of pectin. For 1% pectin, the moisture content is about 0.2% or less. For 5% pectin, the moisture content may be as high as 1%.

The composition thus obtained may be compressed into tablets with conventional tabletting methods and machinery. Optionally the powder or the granules may further be mixed with a lubricant or a mixture of lubricants and then compressed into tablets. If additional lubricant is used it is preferably selected from the group of stearic acid or the magnesium or calcium salt thereof, or glyceryl behenate 45 (Compritol 888 ATO), preferably in an amount of about 0.5 to 4% by weight, calculated to the total weight of the composition. Or the composition may be mixed with excipients. Examples for excipients are dextrinized sucrose (Di Pac sugar), microcrystalline cellulose or starch.

A single tablet as obtained according to the present invention contains preferably 50 mg to 1500 mg, preferably 500 mg to 1000 mg of L-ascorbic acid and/or the pharmaceutically acceptable salt thereof, corresponding to an appropriate daily doses of vitamin C. The following Example illustrates the invention further.

Example

Two pectins having different molecular weight were investigated. One had an average molecular weight of 200 kDalton (USP/100 , lot 02635-0, CP Kelco, San Diego, USA) and another had an average molecular weight of about 350 kDalton. The 350 kDalton pectin was a sample from the United States Department of Agriculture and was prepared by the process disclosed in US Patent 6143337.

A 1.9% pectin solution was prepared by dissolving pectin in water. Sodium ascorbate powder (F. Hoffmann - La Roche AG, Switzerland, Ave. particle size ca. 50 microns) was placed in a Glatt Fluidized-Bed granulator (Model Uniglatt, Switzerland) and sprayed with a fine mist of the pectin solution, which was kept at about 50 °C during spraying. The granulation conditions were as follows:

L-Sodium ascorbate: 400 g

1.9% Pectin solution: 213 g

Pectin solution spraying rate: 9.9 g/minute

Inlet air temperature: 80 °C

Outlet air temperature: 40 °C

Product temperature: 32 °C

The granules had a particle size distribution as shown in Table 1. The granules (125-850 micron fraction) were mixed with the excipients as shown in Table 2 and then compressed into 700-mg tablets with a diameter of 12 mm to tablets of various thickness. The hardness of the tablets was determined and is shown in Table 3.

Table 1

	Particle Size Distribution, %						
Particle Size (Microns)	> 850	> 710	> 500	> 355	> 250	> 125	< 125
Pectin USDA (C99-482)	8.5	6.2	17.2	20.8	21.0	20.2	6.1
Pectin USP100 CP Kelco (lot 02635-0)	15.3	6.1	14.1	16.8	19.8	21.0	7.0

Table 2

	Parts
Granule sample prepared from the example	100
Roche Ascorbic Acid 90% Granulation	65.84
White Di Pac sugar	249.04
Compritol 888 ATO	8.48

Table 3

Pectin USDA (C99-482)		CP Kelco Pectin USP100 (lot 02635-0)	
Mol. Weight : 350 kDalton		Mol. Weight : 200 kDalton	
Tablet Thickness	Tablet Hardness	Tablet Thickness	Tablet Hardness
mm	N	mm	N
4.30	146.6	4.31	134.3
4.15	202.3	4.16	175.5
4.05	238.6	4.04	208.5
3.98	255.0	3.98	234.8
3.94	268.6	3.93	243.1
3.97	297.4	n.a.	n.a.

n.a. : not available

The results of Table 3 show that the use of the high molecular pectin (MW 350 kDalton) resulted in tablets of substantially higher hardness when the same or substantially the same tabletting parameters were applied.

Claims:

1. A composition in the form of a powder or granules comprising:
   (a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof,
   (b) high molecular weight pectin having an average molecular weight of about 300 kDalton or higher and, optionally,
   (c) adjuvants and excipients.

2. A composition according to claim 1, wherein the high molecular weight pectin has an average molecular weight of about 300 kDalton to about 400 kDalton.

3. A composition according to claim 1, wherein the high molecular weight pectin has an average molecular weight of about 350 kDalton.

4. A composition according to any one of claims 1 to 3, wherein the pharmaceutically acceptable salt is sodium L-ascorbate.

5. A composition according to any one of claims 1 to 4, wherein the pectin is present in quantities within the range of about 0.1% to about 10% by weight, calculated on the total weight of the composition.

6. A composition according to any one of claims 1 to 4, wherein the pectin is present in quantities within about 0.5% to about 2% by weight, calculated on the total weight of the composition.

7. A composition according to any one of claims 1 to 6, wherein said composition consists of 95 to 99% by weight of L-ascorbic acid and/or a pharmaceutically acceptable salt thereof and 5 to 1% by weight of pectin, the two components totalling 100% by weight.

8. A composition according to any one of claims 1 to 7, wherein the powder or granules are pressed into a compressed tablet.