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Composition comprising ascorbic acid and pectin

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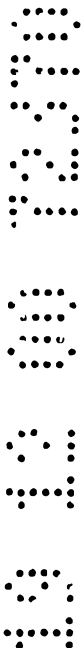
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COMPOSITION COMPRISING ASCORBIC ACID AND PECTIN

Abstract

5 The invention relates to compositions in the form of a powder or granules comprising L-ascorbic acid and/or a pharmaceutically acceptable salt thereof, and pectin in a quantity within the range of about 0.1 to about 10% by weight.



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Invention Title:

Composition Comprising Ascorbic Acid and Pectin

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

5 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, together with pectin. The composition according to the present invention is directly compressible into tablets with good taste, sufficient mechanical strength and hardness, with excellent color stability and is free of
10 sugar and starch. The addition of adjuvants and excipients to the composition for producing tablets is optional.

 Different methods have been suggested for producing L-ascorbic acid powder or granules which are directly compressible into tablets. Hydroxypropylmethylcellulose
15 (HPMC) and starch are today considered as the standard binders for producing such powders and granules. For sugar-free and starch-free tablets, the powder or granules is generally produced with HPMC as binder, although the color stability of such powders or granules, and tablets obtained therefrom, is not sufficient.

20 It was now found that a composition containing L-ascorbic acid and/or its salts together with pectin, may be obtained in the form of a powder or of granules with greatly improved color stability. Tablets made from such compositions have good taste, mechanical strength, and/or hardness, and in addition surprisingly have greatly improved color stability. In such a composition the pectin preferably is present in a
25 quantity with in the range of about 0.1 to about 10% by weight, calculated on the total weight of the composition.

 In one aspect, the present invention relates to a composition in the form of a powder or granules comprising:
30 (a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof,
(b) pectin in a quantity within the range of about 0.1 to about 10% by weight, calculated to the total weight of the composition thereof, and
(c) optionally, adjuvants and excipients in quantities within the range of 0.1 to 10%
by weight, calculated to the total weight of the composition.

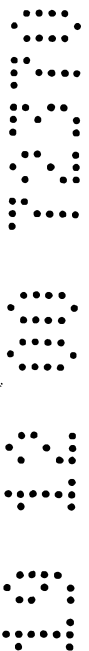
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In a second aspect, the present invention relates to tablets obtained from the composition of the first aspect of the present invention described above.

A third aspect of the present invention provides a process for preparing a composition of the first aspect of the present invention, said process comprising preparing
5 an aqueous slurry of all the components, and spray-drying the slurry in a manner known per se.

A fourth aspect of the present invention provides a process for preparing a composition of the first aspect of the present invention, said process comprising forming a
10 fluidized bed of L-ascorbic acid and/or or a pharmaceutically acceptable salt thereof within a fluidized-bed drying device fitted with spray means, said fluidized bed being fluidized by air or inert gas, and spraying pectin as well as optional adjuvants which are dissolved in an appropriate amount of water in the form of an atomized mist onto the fluidized particles until the desired amount of the pectin binder has been deposited onto the fluidized particles.

15 A fifth aspect of the present invention provides a composition produced by the processes of the third or fourth aspects of the present invention.



5 L-ascorbic acid is known *per se*. Numerous pharmaceutically acceptable salts thereof are known. Preferred from these is sodium ascorbate.

Pectin is a polysaccharide and described for example in the book entitled Industrial Gums, third edition, Academic Press, Inc., 1993, pages 257ff. Commercial
10 pectins are generally produced from either citrus peel or apple pomace. Other possible sources are sugarbeet, sunflower and mango. Preferred pectins to be used within the scope of the present invention are citrus pectins, which generally have lighter color than apple pectins and, thus, do not impart significant color to the granule product.

15 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
20 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.

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

30 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 25 to 50% 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 750 micron.

The composition thus obtained may be compressed into tablets with conventional tableting 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), micro-crystalline 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 examples illustrate the invention.

Example 1

L-ascorbic acid crystals (2475 g, Roche Ascorbic Acid Fine Granular, F. Hoffmann - La Roche AG.), was placed in a stainless container of a wet granulator (Ultra Power model from KitchenAid, Michigan, USA). Pectin (27.36 g, Pectin USP, Danisco Ingredients, Denmark) was dissolved in distilled water (350 g). The pectin solution (151.3 g) was added to the ascorbic acid crystals over a period of 10 minutes

with mixing. After the addition of pectin solution, the paste was mixed for another 10 minutes and then pressed through a screen with 2mm-openings to form a noodle-like particles, which was dried in trays in a 45°C / 25% relative humidity (RH) room for 4 hours. The dry particles were milled and sieved to give the particle size distribution as shown in Table 1A.

Table 1A

Particle size, micron	%
> 710	0.7
> 500	16.2
> 355	29.8
> 250	19.9
> 125	21.9
< 125	11.4
Total	100

10 The granules were mixed with other excipients as shown in the following Table 1B and compressed at 20 KN to give 786 mg tablets. The hardness of the tablet was 88N.

15 Table 1B

	Parts by weight
Granule Sample	108.64
Roche Ascorbic Acid 90% Granulation	79.66
White Di Pac sugar	301.27
Compritol 888 ATO	10.43

To evaluate the color stability, the granules were dried at 45 °C to about 0.08% moisture content, sealed in aluminum bags and stored at ambient temperature. The Whiteness Index (CIE) of the granules was determined at various time intervals using a Hunterlab Ultrascan B256 (Hunter Associates Laboratory, Inc. Reston, VA. USA). For

comparison, the reduction in whiteness index was obtained by subtracting the whiteness indices determined at various storage times from the initial whiteness index. Granules with poor color stability show high whiteness index reduction.

5 Color Stability: Whiteness Index reduction: 1.07 (after 1 month), 2.70 (after 2 months)

Example 2

10 Example 1 was repeated with the exception that Hydroxypropylmethyl-cellulose (HPMC)(Methocel E15LV, The Dow Chemical Co., Michigan, USA) was used in place of pectin. The granule particle size distribution was as given in Table 2.

Table 2

Particle size, micron	%
> 710	0.3
> 500	14.4
> 355	35.0
> 250	23.2
> 125	19.8
< 125	7.4
Total	100

15 Compressed at 20 KN compression force, the hardness of the tablet was 75 N.

The color stability was determined according to Example 1. Color Stability: Whiteness Index reduction: 8.49 (after 1 month temperature), 27.1 (after 2 months).

20 A comparison of the tablets obtained according to Example 1 with those obtained according to Example 2 shows that granules or powder made with pectin as binder are far superior to preparations made with HPMC with regard to tableting compressibility and color stability.

Example 3

5 Sodium L-ascorbate (F. Hoffmann - La Roche AG, Switzerland, particle size etc) was used. A pectin solution was prepared by dissolving 27.3 g of pectin (Pectin USP, 8.4% moisture content, Danisco Ingredients, Denmark) in 1000 g of water. Sodium ascorbate powder was placed in a Glatt Fluidized-Bed granulator (Model Uniglatt, Switzerland) and sprayed with a fine mist of pectin solution. The granulation
10 conditions were as follows:

- L-Sodium ascorbate: 594 g
- Pectin solution: 246.6 g
- Pectin solution spraying rate: 6.7 g/minute
- Inlet Air temperature: 80 °C

15

a) The granules leaving the apparatus had a moisture content of 0.19% by weight, calculated to the granule weight. The granule particles were sieved to give the particle size distribution as shown in Table 3A

Table 3A

Particle size, micron	%
> 710	12.16
> 500	18.03
> 355	22.90
> 250	16.42
> 125	16.82
< 125	13.67
Total	100

20

b) The granules (125-750 micron fraction) as obtained above in Example 3 were mixed with the excipients as shown in the following Table 3B and compressed into tablets of 767 mg weight.

25

Table 3B

	Parts
Sample	108.64
Roche Ascorbic Acid 90% Granulation	79.66
White Di Pac sugar	301.27
Compritol 888 ATO	10.43

5 The tablet hardness at various compression forces is as follows:

Hardness (Compression Force): 118 N (5 KN), 145 N (10 KN), 174 N (15 KN),
203 N (20 KN), 224 N (25 KN), 246 N (30 KN)

10 Example 4

Example 3 was repeated with the exception that Hydroxypropylmethyl-cellulose (HPMC)(Pharmacoat, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) was used in place of pectin.

15 The granulation conditions were as follows:

L-Sodium ascorbate: 594 g

HPMC solution: 246.6 g

HPMC solution spraying rate: 6.7 g/minute

Inlet Air temperature: 80 °C

20

The granule particles were sieved to give the particle size distribution as shown in Table 4

25

Table 4

Particle size, micron	%
> 710	0.2
> 500	1.5
> 355	5.2
> 250	17.5
> 125	58.9
< 125	11.1
Total	100

5 The granules (125-750 micron fraction) were mixed with the excipients and compressed into tablets of 767 mg weight.

 The tablet hardness at various compression forces is as follows:

10 Hardness (Compression Force): 95 N (5 KN), 132 N (10 KN), 151 N (15 KN), 179 N (20 KN), 177 N (25 KN), 200 N (30 KN).

 A comparison of Example 3 with Example 4 shows that granules or powder made with pectin as binder are far superior to preparations made with HPMC with regard to tableting compressibility.

15

The claims defining the invention are as follows:

1. A composition in the form of a powder or granules comprising:
 - (a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof,
 - (b) pectin in a quantity within the range of about 0.1 to about 10% by weight,
5 calculated on the total weight of the composition thereof, and
 - (c) optionally, adjuvants and excipients in quantities within the range of 0.1 to 10% by weight, calculated on the total weight of the composition.
2. A composition according to claim 1, wherein the pharmaceutically acceptable salt of L-ascorbic acid is sodium ascorbate.
- 10 3. A composition according to claims 1 or 2, wherein the pectin is a citrus pectin.
4. A composition according to any one of claims 1 to 3, wherein the pectin is present in quantities within the range of about 0.5% to about 5% by weight, calculated on the total weight of the composition.
- 15 5. A composition according to any one of claims 1 to 3, wherein the pectin is present in quantities within about 0.5% to about 2% by weight, calculated on the total weight of the composition.
6. A composition according to any one of claims 1 to 5, wherein said composition consists of 95 to 99% by weight of L-ascorbic acid and/or a
20 pharmaceutically acceptable salt thereof and 5-1% by weight of pectin, the two components totalling 100% by weight.
7. A composition in the form of a powder or granules comprising:
 - (a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof,
 - (b) pectin in a quantity within the range of about 0.1 to about 10% by weight,
25 calculated on the total weight of the composition thereof, and
 - (c) optionally, adjuvants and excipients in quantities within the range of 0.1 to 10% by weight, calculated on the total weight of the composition, substantially as hereinbefore described with reference to Example 1 or Example 3.
8. A composition according to any one of claims 1 to 7 in the form of a
30 compressed tablet.
9. A composition according to claim 8, containing a lubricant or a mixture of lubricants.

10. The composition according to claim 8 wherein said lubricant or mixture of lubricants is selected from the group of stearic acid or the magnesium or calcium salt thereof, or glyceryl behenate 45 (Compritol 888 ATO).

11. The composition according to claim 8 or claim 9 wherein said lubricant or mixture of lubricants is present in an amount of about 0.5 to 4% by weight, calculated to the total weight of the composition.

12. A composition according to any one of claims 8 to 11, further containing excipients.

13. A composition according to claim 12 wherein said excipients are selected from dextrinized sucrose (Di Pac sugar), microcrystalline cellulose or starch.

14. A tablet containing a composition according to any one of claims 1 to 7.

15. A tablet containing a composition in the form of a powder or granules comprising:

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

(b) pectin in a quantity within the range of about 0.1 to about 10% by weight, calculated on the total weight of the composition thereof, and

(c) optionally, adjuvants and excipients in quantities within the range of 0.1 to 10% by weight, calculated on the total weight of the composition, substantially as hereinbefore described with reference to Example 1 or Example 3.

16. A tablet containing a composition in the form of a powder or granules comprising:

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

(b) pectin in a quantity within the range of about 0.1 to about 10% by weight, calculated on the total weight of the composition thereof, and

(c) optionally, adjuvants and excipients in quantities within the range of 0.1 to 10% by weight, calculated on the total weight of the composition, together with a lubricant or a mixture of lubricants and an excipient, substantially as hereinbefore described with reference to Example 1 or Example 3.

17. A process for preparing a composition according to any one of claims 1 to 13, which comprises preparing an aqueous slurry of all the components, and spray-drying the slurry in a manner known per se.

18. The process according to claim 17 wherein said aqueous slurry has a solid content of about 10 to 70% by weight.

19. The process according to claim 18 wherein said solid content is about 25 to 50% by weight.

20. A process for preparing a composition in the form of a powder or granules comprising:

- 5 (a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof,
(b) pectin in a quantity within the range of about 0.1 to about 10% by weight, calculated on the total weight of the composition thereof, and
(c) optionally, adjuvants and excipients in quantities within the range of 0.1 to 10% by weight, calculated on the total weight of the composition, which comprises
10 preparing an aqueous slurry of all the components, and spray-drying the slurry in a manner known per se, substantially as hereinbefore described with reference to Example 1.

21. A composition when prepared according to the process of any one of claims 17 to 20.

- 15 22. A process for preparing a composition according to any one of claims 1 to 13, which comprises forming a fluidized bed of L-ascorbic acid and/or a pharmaceutically acceptable salt thereof within a fluidized-bed drying device fitted with spray means, said fluidized bed being fluidized by air or inert gas, and spraying pectin as well as optional adjuvants which are dissolved in an appropriate amount of water in the form of an
20 atomized mist onto the fluidized particles until the desired amount of the pectin binder has been deposited onto the fluidized particles.

23. A process for preparing a composition in the form of a powder or granules comprising:

- 25 (a) L-ascorbic acid and/or a pharmaceutically acceptable salt thereof,
(b) pectin in a quantity within the range of about 0.1 to about 10% by weight, calculated on the total weight of the composition thereof, and
(c) optionally, adjuvants and excipients in quantities within the range of 0.1 to 10% by weight, calculated on the total weight of the composition, said process
30 comprising forming a fluidized bed of L-ascorbic acid and/or or a pharmaceutically acceptable salt thereof within a fluidized-bed drying device fitted with spray means, said fluidized bed being fluidized by air or inert gas, and spraying pectin as well as optional adjuvants which are dissolved in an appropriate amount of water in the form of an atomized mist onto the fluidized particles until the desired amount of the pectin binder

has been deposited onto the fluidized particles, substantially as hereinbefore described with reference to Example 3.

24. A composition when prepared according to the process of claim 22 or claim 23.

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