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(54) Title: TABLETS OF STEVIA EXTRACT AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The technical field of the present invention relates to a sweetener tablet of stevia extract prepared by direct compression method.
Description

TABLETS OF STEVIA EXTRACT AND PROCESSES FOR THEIR PREPARATION

[1] Technical Field of Invention

The technical field of the present invention relates to sweetener tablets of stevia extract prepared by direct compression processes.

[2] Background of the Invention

*Stevia rebaudiana* Bertoni is a perennial shrub of the Asteraceae (Compositae) family native to Paraguay and Brazil. Leaves of *Stevia rebaudiana* are well known for their sweetening properties. The sweet compounds are mainly the diterpene glycosides based on the kaurene skeleton that represent about 14% constituent of dried leaves. The sweet diterpene glycosides include stevioside, steviolbioside, rebaudioside A, B, C, D, and E, and dulcoside A and B. Steviol is the aglycone moiety in all these glycosides. Among these, the major sweet components are stevioside, which has a molecular weight of 804.9 and a melting point between 196-198°C, and rebaudioside A, which has a molecular weight of 967.0 and a melting point between 242-244°C.

[3] *Stevia rebaudiana* extract is widely accepted as a food for use as a dietary supplement and also as a natural sweetener worldwide, particularly in food and beverages. The major component, stevioside, is heat and pH stable. It is approximately three hundred times sweeter than sucrose, and has zero calorific value. It has been used for more than twenty years in Japan with no adverse effects reported so far. However, stevioside, apart from its high level of sweetness, also has the inherent property of an unpleasant and undesirable menthol like bitter aftertaste. The unpleasant taste is also contributed to by volatile aromatic or essential oils, tannins, and flavonoids present in Stevia leaf extract (*Stevia* extract).

[4] Sweetener compositions of stevia extract are disclosed in various publications. For example, Japanese patent 3046763 discloses irregular shaped cubes of stevioside that may be readily mixed in beverages like coffee and tea. Laid open Japanese patent application 4287659 discloses powder compositions of stevioside mixed with polydextrose, maltitol, erythritol and thaumatin. Japanese patent 53044666 discloses sweetener compositions of stevioside and maltitol for use in low-calorie gelatin jelly.

[5] Stevia extract is fluffy in nature and therefore difficult to compress into tablets as such using conventional tableting techniques involving aqueous, non-aqueous granulation. The tablets develop problems of capping and sticking, and disintegrate slowly, all of which are undesirable characteristics. Further, direct compression of fine stevia extract particles leads to excessive sticking.
Summary of the Invention

In one general aspect there is provided a directly compressed sweetener tablet of stevia extract that includes particles of stevia extract, wherein at least 40% of the particles of stevia extract have a size greater than 100 μm.

Embodiments of the directly compressed sweetener tablet may include one or more of the following features. For example, at least 40% of the particles of the stevia extract may be greater than 100 μm and none of the particles of stevia extract greater than 500 μm. At least 40% of the particles of stevia extract may be greater than 150 μm.

The amount of stevia extract in the tablet may be from about 5% w/w to about 50% w/w. The stevia extract may be from about 15% w/w to about 25% w/w.

The stevia extract may include stevioside. The stevia extract may be made up of at least 30% w/w stevioside.

The stevia extract may further include rebaudioside A. The stevia extract may be at least 10% w/w rebaudioside A.

The tablet may further include one or more inert excipients. The one or more inert excipients may be one or more of flavors, disintegrants/superdisintegrants, binders, fillers, suspending agents, surfactants, colors, and lubricants/ glidants. The flavor may be maltol and/or any other FEMA/GRAS approved flavor for oral use.

The tablet may disintegrates in water in less than about 180 seconds, and more particularly in less than about 60 seconds. The tablet may have a hardness of at least 1 kg.

The tablet may further include an active pharmaceutical ingredient.

In another general aspect there is provided a process of preparing directly compressed sweetener tablets wherein the process includes blending stevia extract having at least 40% of particles greater than 100 μm with one or more inert excipients and compressing into tablets. Embodiments of the process may include any one or more of the features described above or herein.

In another general aspect there is provided a pharmaceutical composition that includes an active pharmaceutical ingredient and stevia extract, wherein the stevia extract comprises particles and at least 40% of the particles of stevia extract have a size greater than 100 μm. Embodiments of the pharmaceutical composition may include one or more of the following features or those described above. For example, the pharmaceutical composition may further comprise one or more pharmaceutically acceptable excipients.

In another general aspect there is provided a method of treating a medical condition, the method comprising administering a pharmaceutical composition comprising an active pharmaceutical ingredient indicated for the medical condition and stevia extract, wherein the stevia extract comprises particles and at least 40% of the particles of stevia
extract have a size greater than 100 μm. Embodiments of the method of treatment may include any one or more of the features described above and herein.

[20] 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.

[21] **Detailed Description of the Invention**

[22] We have now surprisingly discovered that sweetener tablets of stevia extract having acceptable disintegration properties may be prepared by direct compression of stevia extract particles having a desirable size range.

[23] Hence in one general aspect there is provided a directly compressed sweetener tablet of stevia extract comprising at least 40% particles on a weight basis (weight/weight) of stevia extract greater than 100 μm. In another general aspect, there is provided a process for preparing a directly compressed sweetener tablet wherein the process comprises the steps of blending stevia extract having at least 40% particles on a weight basis (weight/weight) greater than 100 μm with one or more inert excipients; and compressing into tablets.

[24] The term 'particle size' as used herein refers to the average particle diameter of the particle on conversion of its volume into a sphere. It is to be understood that a reference to having at least 40% particles greater than 100 μm, or other such values, refers to a percentage of particles on a weight basis (weight/weight). For example, the measurement of particle size on a weight basis can be made by sieve analysis.

[25] The present invention relates to a simple and cost effective method of preparing tablets of the poorly compressible stevia extract. Using excessively fine stevia extract particles in the direct compression method leads to excessive sticking during tabletting. Therefore it is important to select the proper particle size. We have found that using particles in a specific size range however solved the problem of sticking and made the processing smooth. Processing losses due to fines also was drastically reduced.

[26] Sweetener tablets of the instant invention comprise stevia extract particles of a particular size range, for example, at least 40% of the stevia extract particles have a particle size greater than 100 μm. In particular, at least 40% of stevia extract particles have a particle size greater than 100 μm, and none of the particles would be greater than 500 μm.

[27] Stevia extract particles of the desired size range may be obtained by the process of sieving using standard size sieves; milling using conventionally-used mechanical mills such as cad mill, fitz mill, multi mill, impact mill, and ball mill; or an air jet mill. In particular, sieving may be used.

[28] The term 'stevia extract' as used herein refers to an aqueous extract obtained from leaves of *Stevia rebaudiana*. It is a white, free flowing, fluffy granular powder having
an extremely sweet taste, and comprising at least 30% w/w stevioside and at least 10% w/w rebaudioside A, and in particular at least 50% w/w stevioside and 20% w/w rebaudioside A. The amount of stevia extract may vary from about 5% w/w to about 50% w/w of the sweetener tablet and, in particular, it may vary from about 15% w/w to about 25% w/w.

[29] In one of the embodiments, the sweetener tablets may comprise stevia extract and one or more inert excipients.

[30] The term 'inert excipient' as used herein includes all physiologically inert excipients used in the art for preparation of sweetener compositions. Examples include flavors, disintegrants/superdisintegrants, binders, fillers, suspending agents, surfactants, lubricants/glidants, colors, and the like.

[31] The bitter aftertaste of stevioside may be masked by inclusion of one or more flavors in the sweetener tablet composition. Examples of flavors include any FEMA/GRAS approved flavor for oral use. In particular, flavors comprising maltol may be used.

[32] Maltol (lариxinic acid) is a white, crystalline compound obtained from larch bark, pine needles, chicory, or roasted malt. Maltol is soluble in water and glycerine, slightly soluble in alcohols and chloroform; and has a melting point of 161°C. Maltol and its derivatives have a caramel-like odor and are used as versatile flavor enhancers and modifiers (sweet, caramel, fruity, strawberry) in foods, wines, and perfumes. Commericially, maltol is available under various trade names, such as Veltol and Pyromaltol. Maltol is also an important constituent of many flavors approved for oral use, for example, Contramarum Forte (Flavour 225023) obtained from Symrise. Besides maltol, Contramarum Forte Flavour comprises maltodextrin, gum arabic, and artificial and natural identical ingredients like menthol esters and food esters. On combining maltol with stevia extract in sweetener tablet compositions, the bitter aftertaste is masked to acceptable limits. Further, maltol is required in very low quantity.

[33] Specific examples of disintegrants/superdisintegrants include starch, cellulose derivatives, natural and synthetic gums, sodium starch glycolate, croscarmellose sodium, crospovidone, and low-substituted hydroxypropylcellulose. Extremely fast disintegration may be achieved by using superdisintegrants in the sweetener tablet.

[34] Specific examples of binders include starch; gelatin; sugars such as molasses, lactose, glucose, dextrose and sucrose; and natural and synthetic gums such as acacia, sodium alginate, carboxymethyl cellulose, methylcellulose, polyvinyl pyrrolidone and veegum.

[35] Specific examples of fillers include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, powdered
cellulose, dextrates, dextrins, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, sucrose, sugar compressible, and sugar confectioners. In particular, microcrystalline cellulose may be used.

[36] Specific examples of suspending agents include microcrystalline cellulose, sodium carboxy methylcellulose, colloidal anhydrous silica, mannitol, povidone, sodium starch glycolate, and veegum.

[37] Specific examples of surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in sweetener compositions. These include polyethoxylated fatty acids and their derivatives, for example, polyethylene glycol 400 distearate, polyethylene glycol -20 dioleate, polyethylene glycol 4 -150 mono dilaurate, polyethylene glycol -20 glyceryl stearate; alcohol - oil transesterification products, for example, polyethylene glycol - 6 corn oil; polyglycerized fatty acids, for example, polyglyceryl - 6 pentaoleate; propylene glycol fatty acid esters, for example, propylene glycol monopropylate; mono and diglycerides, for example, glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and their derivatives, for example, polyethylene glycol - 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example, polyethylene glycol - 20 cetyl ether, polyethylene glycol - 10 - 100 nonyl phenol; sugar esters, for example, sucrose monopalmitate; polyoxyethylene - polyoxypropylene block copolymers known as 'poloxamer'; ionic surfactants, for example, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine.

[38] Specific examples of lubricants/glidants include colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, and white beeswax.

[39] Examples of colors include any approved color for oral use.

[40] In one of the embodiments, sweetener tablets of stevia extract may be prepared by a process that includes the steps of blending stevia extract having at least 40% of particles greater than 100 μm with one or more of filler, superdisintegrant, and lubricant/glidant; and compressing into tablets using appropriate tooling.

[41] In another embodiment, the sweetener tablets prepared above may comprise a flavoring agent, particularly maltol.

[42] Sweetener tablets prepared in any of the embodiments above had a hardness of about 1.5-2.0 kg, and a disintegration time of less than about three minutes and, in particular, less than about one minute.

[43] The invention is further illustrated by the following examples, which are provided for illustrative purpose and should not be construed as limiting the scope of the
invention in any way.

Examples

Sweetener tablet compositions

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight/tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example 1</td>
</tr>
<tr>
<td>Stevia Extract</td>
<td>15.0*</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>-</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>3.00</td>
</tr>
<tr>
<td>Silicon dioxide</td>
<td>0.10</td>
</tr>
<tr>
<td>Flavour 225023</td>
<td>-</td>
</tr>
<tr>
<td>Lactose Anhydrous</td>
<td>30.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.10</td>
</tr>
<tr>
<td>Lactose DCL 21</td>
<td>51.8</td>
</tr>
</tbody>
</table>

* All particles pass through #100 sieve; ** All particles pass through #30 sieve, 40% retained on #100 sieve

Procedure:

1. Croscarmellose sodium, flavour (in example 3), silicon dioxide and stearic acid were individually sieved through a #60 sieve.
2. Stevia extract was sieved through appropriate sieves.
3. Lactose was sieved through a #30 sieve.
4. Sieved croscarmellose sodium, flavour (only Example 3), silicon dioxide and stearic acid of step 1 were blended in a suitable mixer followed by blending with a part of sieved lactose anhydrous powder of step 3.
5. Sieved stevia extract of step 2 was then added to the blend of step 4 and mixed for about 5-10 minutes, followed by blending with the remaining part of lactose anhydrous for about 10-15 minutes.
6. The blend of step 5 was compressed into 100 mg tablets using appropriate toolings.

Compositions as per Example 1 comprising fine stevia extract particles could not be compressed into tablets due to excessive sticking in dies and on punches. However, the compositions of Examples 2 and 3 comprising stevia particles in the desired size range were easily compressed. The tablets thus prepared were tested for hardness using
Monsanto hardness tester, and in vitro disintegration using Electrolab® instrument. The values of the various parameters are listed below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Example 2</th>
<th>Example 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardness</td>
<td>1.5-2.0 Kg</td>
<td>1.5-2.0 Kg</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>43 seconds</td>
<td>48 seconds</td>
</tr>
</tbody>
</table>

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. For example, the stevia extract having a particular size range (e.g., at least 40% particles (w/w) of stevia extract greater than 100 μm) can be combined in a pharmaceutical dosage form with an active ingredient as a taste masking agent. Such pharmaceutical dosage forms can be made using the processes described herein with slight modifications as needed. Maltol can be used in the pharmaceutical compositions as desired. The pharmaceutical composition can be administered to treat a medical condition for which the active pharmaceutical ingredient is indicated or recommended. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.
Claims

[1] A directly compressed sweetener tablet of stevia extract comprising particles of stevia extract, wherein at least 40% of the particles of stevia extract have a size greater than 100 μm.

[2] The directly compressed sweetener tablet of claim 1 wherein at least 40% of the particles of stevia extract are greater than 100 μm and none of the particles of stevia extract are greater than 500 μm.

[3] The directly compressed sweetener tablet of claim 1 wherein at least 40% of the particles of stevia extract are greater than 150 μm.

[4] The directly compressed sweetener tablet of claim 1 wherein the amount of stevia extract in the tablet comprises from about 5% w/w to about 50% w/w.

[5] The directly compressed sweetener tablet of claim 4 wherein stevia extract comprises from about 15% w/w to about 25% w/w.

[6] The directly compressed sweetener tablet of claim 1 wherein the stevia extract comprises stevioside.

[7] The directly compressed sweetener tablet of claim 6 wherein the stevia extract comprises at least 30% w/w stevioside.

[8] The directly compressed sweetener tablet of claim 6 wherein the stevia extract further comprises rebaudioside A.

[9] The directly compressed sweetener tablet of claim 8 wherein the stevia extract comprises at least 10% w/w rebaudioside A.

[10] The directly compressed sweetener tablet of claim 1 wherein the tablet further comprises one or more inert excipients.

[11] The directly compressed sweetener tablet of claim 10 wherein the one or more inert excipient comprise flavors, disintegrants/superdisintegrants, binders, fillers, suspending agents, surfactants, colors, and lubricants/glidants.

[12] The directly compressed sweetener tablet of claim 11 wherein the flavor comprises maltol.

[13] The directly compressed sweetener tablet of claim 1 wherein the tablet disintegrates in water in less than about 180 seconds.

[14] The directly compressed sweetener tablet of claim 13 wherein the tablet disintegrates in water in less than about 60 seconds.

[15] The directly compressed sweetener tablet of claim 1 wherein the tablet has a hardness of at least 1 kg.

[16] The directly compressed sweetener tablet of claim 1 further comprising an active pharmaceutical ingredient.

[17] A process for preparing directly compressed sweetener tablets wherein the
process comprises blending stevia extract having at least 40% of particles greater than 100 μm with one or more inert excipients and compressing into tablets.

[18] A pharmaceutical composition comprising an active pharmaceutical ingredient and stevia extract, wherein the stevia extract comprises particles and at least 40% of the particles of stevia extract have a size greater than 100 μm.

[19] The pharmaceutical composition of claim 18 further comprising one or more pharmaceutically acceptable excipients.

[20] A method of treating a medical condition, the method comprising administering a pharmaceutical composition comprising an active pharmaceutical ingredient indicated for the medical condition and stevia extract, wherein the stevia extract comprises particles and at least 40% of the particles of stevia extract have a size greater than 100 μm.