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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2007 (22.03.2007)

PCT

(10) International Publication Number
WO 2007/030902 A2

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 36/81* (2006.01)
A61K 36/28 (2006.01) *A61K 36/185* (2006.01)

(21) International Application Number:
PCT/BR2006/000183

(22) International Filing Date:
12 September 2006 (12.09.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PI0504985-7 14 September 2005 (14.09.2005) BR

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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, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, 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, LV, 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).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that 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:** IMPROVED PHARMACEUTICAL COMPOSITION CONTAINING ARTICHOKE EXTRACT, AND PROCESS FOR ITS PRODUCTION

(57) **Abstract:** The present invention provides oral solid pharmaceutical compositions useful in the treatment of gastrointestinal tract disorders, through modulation of the hepatic, biliary and gastrointestinal tract motility activities; such improved pharmaceutical compositions are stable and comprise, in a preferred embodiment, dried extracts of artichoke, boldo and jurubeba, in association with Magnesium Sulphate and Choline Bitartrate; also disclosed is a process of preparation of oral solid pharmaceutical compositions comprising dried artichoke extract, by which the difficulties in the preparation of similar pharmaceutical compositions are overcome.

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Description

Improved Pharmaceutical Composition containing Artichoke Extract, and Process for its Production

Field of the Invention

The present invention is related to pharmaceutical compositions and to processes for its production. More specifically, the compositions of the present invention is oral and solid, and comprises as active principles dry artichoke extracts in association with other active ingredients. In a preferential embodiment of the invention, the composition comprises dry extracts of artichoke, boldo and jurubeba associated with magnesium sulphate and choline bitartrate, acting together as modulating agents of the gastrointestinal tract functions, including hepatic, biliary and gastrointestinal tract motility functions. The compositions of the present invention are stable and presented under the oral solid dosage form, overcoming difficulties of use, storage and production of the previously available compositions.

Background of the Invention

The liver is an organ where several reactions occur, including the synthesis of many enzymes and reactions related to body detoxication. Therefore, the liver is very important to the health of the individual. Since the middle of the 16th century, several books and scientific works about medicinal plants provide knowledge about innumerable useful plants which act as liver therapeutical agents, including boldo (*Peumus boldus*) and artichoke (*Cynara scolymus*).

In folk medicine, the artichoke is recommended for the treatment of indigestions caused by inadequate bile production, being also indicated as liver medicine and as cholagogue. It is generally used in aqueous alcoholic extract. The artichoke also provides significant diuresis, grounding its use as a dehydrating agent. On the other hand, artichoke leads to improved elimination of uric acid salts, grounding its use as an antirheumatic agent. In 1934, one of

the first compounds having biological activity were isolated from artichoke leaves. In 1954, cynarine was identified and although absent from the extract it is produced during processing of the plant, when heated in aqueous environment. Some important composite classes present in the artichoke are flavonoids and caffeoylquinic acids. For pharmaceutical intentions, some compositions were developed using generally basal leaves because they comprise higher levels of choleretic active principles. The composition of the present invention differs from the currently available artichoke compositions due to the fact that these compositions have artichoke associated with sorbitol (Miller), or artichoke associated with boldo (Vitamed/Herald's/Simões).

The composition of the present invention comprises as active principles dry extracts of artichoke, boldo and jurubeba associated with magnesium sulphate and choline bitartrate. This composition displayed very good results in clinical trial conducted at Grafée Guinle Hospital, in Rio de Janeiro, and filed in the Ministry of health (results not yet published). In addition, the composition of the present invention required the development of new excipients to enable direct compression.

According to what will be demonstrated in the following documents, there had not been found reports of compositions, formulations or production processes which anticipate the present invention.

Document US 2002/012708 discloses medicines based on vegetal extracts, in special the dry artichoke extract to decrease glucose, creatinine and/or bilirubin blood levels, for immunostimulation, leucopenia, granulocytopenia and linfocytopenia therapies and tissues or organs damages caused by kidneys, liver, pancreas, bladder infections, etc. However, the composition described in this document doesn't use the dry artichoke extract and its formulation requires the use of adjuvant ingredients, like lipotropic agents.

Document US 2003/044512 discloses a liver nutritional composition, containing vegetal extracts and adjuvants, such as amino acids and vitamins, which protects the liver against damages and promotes its regeneration, as well

as improves its function. However, the composition described in this document neither discloses use the combination of dry artichoke extract with the associations of the present invention nor contains Magnesium Sulphate and Choline Birtartrate.

Document WO 00/19973 describes compositions containing boldo extract to be used in cosmetic and/or dermatological preparations. However, such preparations don't aim any modulating action of the gastrointestinal tract activity and don't contemplate formulations such as the ones disclosed by the present invention.

Document GB 912738 describes compositions with cholagogue and/or choleretic activities. However, such activity is due to cynnamic acid derivatives, and there isn't any mention neither to vegetal extracts nor to formulations such as the ones disclosed by the present invention.

Although compositions with the same purpose of those of the present invention are currently available, such compositions are different and present limitations: (i) the compositions in liquid form have several disadvantages related to stability and to difficulties in the production and use; and (II) the ones available in dry form don't use the dry artichoke extract in combination with the associations of the present invention, and don't comprise neither Magnesium Sulphate nor Choline Bitartrate, and also present many stability problems, like hygroscopicity, which makes the production difficult and its shelf-life smaller. These and other difficulties were successfully overcome by the compositions of the present invention, and by its preparation process, in order to make available stable solid formulations containing vegetal extracts and chemical substances acting together as cholagogues, choleretics, hepatoprotectors, etc to modulate the gastrointestinal function.

Summary of the Invention

It is an object of the present invention to provide an improved pharmaceutical composition containing modulating agents of gastrointestinal

tract functions executing therapeutical actions on the hepatic and biliary functions and on the gastrointestinal tract motility.

In another object of the present invention, an oral solid pharmaceutical composition comprising as active principles dry artichoke extracts in association with selected ingredients of the group that consists of: hepatoprotector agents, cholagogues, laxatives, stimulants of the digestive function, lipotropic and/or gastrointestinal motility agents, or combinations thereof. In a preferred embodiment, the oral solid pharmaceutical composition comprises as active principles dry extracts of artichoke, boldo and jurubeba, in association with Magnesium Sulphate and Choline Bitartrate.

In another aspect, being, therefore, another object of the present invention is provided an oral solid pharmaceutical composition endowed with improved stability.

In another aspect of the present invention, being, therefore, another of its objects, a process of preparation of an oral solid pharmaceutical composition containing dry artichoke extract is provided, overcoming the difficulties of previous preparation process of similar pharmaceutical compositions.

These and other objects of the present invention will be more evident from the detailed description of the invention and the attached claims.

Detailed Description of the Invention

The present invention comprises pharmaceutical compositions containing modulator agents of the gastrointestinal tract functions. For the purposes of the present invention, the expression "gastrointestinal tract functions" comprises the activities played by the liver, bile and the gastrointestinal motility. Many studies showed that some ingredients can play more than one role, acting, for example, as modulator of the biliary secretion and as hepatoprotector.

In this technology field, where medicines comprising artichoke extracts are used, the administration route normally is carried through oral liquids. However, this method presents some inconveniences when used, as will be commented. The oral liquids can be presented in the form of extracts,

dispersions and emulsions in which the active principle is diluted together with other pharmacologic excipients used in the formulation. This therapeutical administration method is widely used for pediatric or geriatric use, when the users may have difficulties on the medicine ingestion. However, the oral liquids present the disadvantage of the having a considerable volume, making its container difficult to be transported when there is necessity of user locomotion. Moreover, the content has to be homogenized before the use and also has to be correctly dosed, using an appropriate and previously clean measuring device. Another peculiar disadvantage of this administration route is the expiration time of the medicine which, for being in the liquid form, is more susceptible to biological and/or chemical degradation than if it were in solid and/or dried form. Therefore, proposing an efficient alternative, allied to the practicity, economy and security, the inventors had developed the present invention, which consists of a new composition of active principles in solid and/or dried form.

The administration in the solid and/or dried form is efficient in many aspects, because it facilitates the ingestion of the medicine in different dosages without requiring volume measurements. Moreover, the solid and/or dried form provides the advantage of being compact and easy to transport, being able to be taken in the pocket. The solid and/or dried form of the present invention demonstrated a lower microbial growth susceptibility during the storage time, favoring the conservation of the medicine and its respective validity. The solid and/or dried form can be presented as a tablet containing a core with a composition based on the active ingredients, used individually or collectively with pharmaceutically acceptable and conventionally used ingredients, such as disintegrant excipients (sodium *crosscarmellose* or another), lubricant (magnesium stearate or another), agglutinants (microcrystalline cellulose or another) and binders (povidone k-30 or another).

The present invention comprises oral solid pharmaceutical compositions containing as active principles dry artichoke extracts in association with ingredients selected from the group consisting of: hepatoprotector agents,

cholagogues, laxatives, stimulants of the digestive function, lipotropic and/or of gastrointestinal motility agents, or combinations thereof. Artichoke extracts (*Cynara scolymus L.*) are known for its diuretic activities, promoting greater water elimination due to the increase of diuresis. The association of these extracts with the above-mentioned ingredients provides synergic effects, being the mechanism of action of the additional ingredients detailed below.

A) Cholagogues – Biliary Secretion Modulators

The biliary secretion modulators are generally known as cholagogues, which are responsible for the increase of the bile and/or choleretic flow, that are responsible for the increase of the production of bile. Some examples of cholagogues generally used are the extracts of plants, such as, *Achillea millefolium*, *Arctium lappa*, *Baptisia tintoria*, *Berberis vulgaris*, *Calendula officinalis*, *Chelidonium majus*, *Chionanthus virginicus*, *Curcuma longa*, *Cynara scolymus*, *Gentiana lútea*, *Lavendula angustifólia*, *Mentha piperita*, *Rheum officinalis*, *Rosmarius officinalis*, *Sanguinaria canadensia*, *Schisandra chinensis*, *Stillingia sylvatica*, *Taraxacum officinale*, *Verbena officinalis*, *Solanum paniculatum L.*

B) Gastrointestinal Motility Modulators

The gastrointestinal motility modulators can be subdivided in 2 classes: laxatives and producers of constipation. Laxatives are substances that increase the peristalsis, promoting the regular movement of excrements. Many substances can act in this way, such as alimentary fibers, fibers of *Psyllium* (*Plantago ovata*) (volume laxatives); glycerin, mineral oil, sodium docusate (laxative emollients); poor absorbed sugars, magnesium salts, polyethyleneglycol (osmotic laxatives); and extracts of plants rich in anthraquinones (*Rhamnus purshiana*, *Senna sp*), preparations containing diphenylmethane (stimulant laxatives). The agents who promote constipation decrease peristalsis, causing coprostasis. Several substances present such characteristic, including: anticholinergic agents (antidepressants, antipsychotic and antiparkinsonian); cations containing agents (aluminum, calcium, bismuth

and iron salts, sucralfate); and others, such as the calcium channel blockers, diuretics, anti-inflammatories, opioids substances, clonidine, ganglion blockers.

C) Hepatoprotectors: Hepatic Activity Modulators

Substances which protect the liver and stimulate cell regeneration include vegetal extracts such as extracts of *Peumus boldo*, *Solanum paniculatum*, *Silybum marianum.*

D) Lipotropic Agents

Lipotropic agents help on the reduction of the cholesterol blood levels, stimulate lecithin production and reduce production of fat in the liver and rest of the body. Some lipotropic agents generally used are methionine and choline bitartrate.

The following examples must be understood as illustratives, not limiting possible further embodiments of the invention.

Example 1 – Used ingredients

In a preferred embodiment of the present invention, the oral solid composition comprises dry artichoke extracts, boldo and jurubeba, in association with Magnesium Sulphate and Choline Bitartrate. Table I presents the ingredients, their concentrations and their respective functions in the composition of the present invention.

Table I – Fomulation

Ingredients	Amount (mg/tablet) (SI)	Functions
Artichoke dry extract (*Cynara scolymus* L.)	100,000	Choleretic, cholagogue, diuretic
Jurubeba dry extract (*Solanum paniculatum* L.)	50,000	Hepatoprotector, cholagogue, laxative
Boldo dry extract (*Peumus boldus* (Molina) Lyons)	50,000	Hepatoprotector, stimulant of the digestive functions
Monohydrated Magnesium Sulphate	100,000	Intestinal motility agent
Choline Bitartrate	10,000	Lipotropic Agent
Microcrystalline Cellulose	73,300	Diluent
Corn Starch	16,900	Diluent
Polividone	17,400	Binder
Sodium Croscarmellose	8,700	Disintegrant
Silicon Dioxide	4,350	Lubricant/Adsorbent

Magnesium Stearate	4,350	Lubricant
Shellac	2,000	Tableting Excipient
Ethyl Alcohol	—	Solvent
Talc	18,700	Tableting Excipient
Refined Sugar	334,290	Tableting Excipient
Ponceau Red	1,720	Stain
Titanium Dioxide	1,190	Tableting Excipient
Arabic Gum	6,900	Tableting Excipient
Beeswax	0,100	Tablet Polishing Excipient
Carnauba Wax	0,100	Tablet Polishing Excipient
Chloroform	—	Solvent
Purified Water	—	Solvent

Example 2 - Process of Manufacture

The compositions of the present invention, such as, for example, the one described in Table I, can be prepared by a process that comprises the following steps:

- Homogenization of the active ingredients (Artichoke Extract, Boldo Extract, Jurubeba Extract, Magnesium Sulphate, Choline Bitartrate) in a fast Granulator Mixer until complete homogenization;

- Addition of an auxiliary granulation solution (for example, polividone in purified water) to the previously mixed powders in the fast Granulator Mixer, followed by homogenization until the desired point of granulation is reached; and

- Drying of the moist granulated material until the moisture specification of the granule is reached.

The dried and granulated material can be encapsulated by processes known in the state of the art. Optionally, the dried and granulated material obtained at the previous step can be tabletted. Therefore, an additional step is required, adding magnesium stearate, sodium croscarmellose and silicon dioxide (additive of tabletting) to the dried and homogenized pellet of the previous step, of followed by complete homogenization; and

- Compression of the mixture previously obtained, by the processes known in the state of the art, optionally followed by coating, coloration and polishing in adequate equipments.

Tests carried by the inventors had indicated that the formulation developed specifically for the compression/tabletting of this pharmaceutical composition overcome the previously existing difficulties on the preparation process, such as the extreme hygroscopicity and the necessity of frequent maintenance of the tabletting machine.

It's important to mention that small variations on the form of execution of the invention must be understood as being inside of the scope of the invention and the attached claims.

Claims

Improved Pharmaceutical Composition containing Artichoke Extract, and Process for its Production

1. Improved oral solid pharmaceutical composition for the treatment of gastrointestinal tract disorders characterized by comprising:
   - dry extract of *Cynara scolymus*; and
   - at least one substance selected from the group consisting of hepatoprotectors, cholagogues, gastrointestinal motility modulators, lipotropic agents and mixtures thereof.

2. Pharmaceutical composition, according to claim 1, characterized by the fact that the hepatoprotectors are selected from the groups consisting of extract of *Peumus boldo*, extract of *Solanum paniculatum*, extract of *Silybum marianum* and mixtures of the same.

3. Pharmaceutical composition, according to claim 1, characterized by the fact that the cholagogues are selected from the group comprising extract of *Achillea millefolium*, extract of *Arctium lappa*, extract of *Baptisia tintoria*, extract of *Berberis vulgaris*, extract of *Calendula officinalis*, extract of *Chelidonium majus*, extract of *Chionanthus virginicus*, extract of *Curcuma longa*, extract of *Gentiana lútea*, extract of *Lavendula angustifólia*, extract of *Mentha piperita*, extract of *Rheum officinalis*, extract of *Rosmarius officinalis*, extract of *Sanguinaria canadensia*, extract of *Schisandra chinensis*, extract of *Stillingia sylvatica*, extract of *Taraxacum officinale*, extract of *Verbena officinalis*, extract of *Solanum paniculatum L.* and mixtures thereof.

4. Pharmaceutical composition, according to claim 1, characterized by the fact that the gastrointestinal motility modulators are selected from the group consisting of laxatives and producers of constipation.

5. Pharmaceutical composition, according to claim 4, characterized by the fact that the laxatives are selected from the group consisting of as alimentary fibers, fibers of *Psyllium* (*Plantago ovata*), glycerin, mineral oil, sodium docusate, poor absorbed sugars, magnesium salts, polyethyleneglycol, extracts of plants rich in anthraquinones such as *Rhamnus purshiana*, *Senna sp*, diphenylmethane, and mixtures thereof.

6. Pharmaceutical composition, according to claim 4, characterized by the fact that the producers of constipation are selected from the group consisting of anticholinergic agents, such as antidepressants, antipsychotic and antiparkinsonian; cations containing agents such as aluminum, calcium, bismuth and iron salts; sucralfate, calcium channel blockers, diuretics, anti-inflammatories, opioids substances, clonidine, ganglion blockers and mixtures thereof.

7. Pharmaceutical composition, according to claim 1, characterized by the fact that the lipotropic agents are selected from the group consisting of methionine, choline bitartrate and mixtures thereof.

8. Process for the preparation of an oral solid pharmaceutical composition for the treatment of gastrointestinal tract disorders characterized by comprising the steps of:

a) homogenization of an effective amount of extract of *Cynara scolymus* and an effective amount of at least one substance selected from the group consisting of hepatoprotectors, cholagogues, gastrointestinal motility modulators, lipotropic agents and mixtures thereof; in a fast granulator mixer;

b) addition of an auxiliary granulation solution to the previously mixed powders in the fast granulator mixer, followed by homogenization until the desired point of granulation is reached; and

c) drying of the moist granulated material.

9. Process, according to claim 8, characterized by further comprising the steps of:

d) addition, to the dried and homogenized pellet, of a lubricant and/or adsorbent, followed by complete homogenization;

e) compression of the mixture previously obtained; and

f) optionally coating, coloring and/or polishing.

10. Process, according to claims 8 and 9, characterized by the fact that the hepatoprotectors are selected from the groups consisting of extract of *Peumus boldo*, extract of *Solanum paniculatum*, extract of *Silybum marianum* and mixtures of the same.

11. Process, according to claims 8 and 9, characterized by the fact that the cholagogues are selected from the group comprising extract of *Achillea millefolium*, extract of *Arctium lappa*, extract of *Baptisia tintoria*, extract of *Berberis vulgaris*, extract of *Calendula officinalis*, extract of *Chelidonium majus*, extract of *Chionanthus virginicus*, extract of *Curcuma longa*, extract of *Gentiana lútea*, extract of *Lavendula angustifólia*, extract of *Mentha piperita*, extract of *Rheum officinalis*, extract of *Rosmarius officinalis*, extract of *Sanguinaria canadensia*, extract of *Schisandra chinensis*, extract of *Stillingia sylvatica*, extract of *Taraxacum officinale*, extract of *Verbena officinalis*, extract of *Solanum paniculatum L.* and mixtures thereof.

12. Process, according to claims 8 and 9, characterized by the fact that the gastrointestinal motility modulators are selected from the group consisting of laxatives and producers of constipation.

13. Process, according to claim 12, characterized by the fact that the laxatives are selected from the group consisting of as alimentary fibers, fibers of *Psyllium* (*Plantago ovata*), glycerin, mineral oil, sodium docusate, poor absorbed sugars,

magnesium salts, polyethyleneglycol, extracts of plants rich in anthraquinones such as *Rhamnus purshiana*, *Senna sp*, diphenylmethane, and mixtures thereof.

14. Process, according to claim 12, characterized by the fact that the producers of constipation are selected from the group consisting of anticholinergic agents, such as antidepressants, antipsychotic and antiparkinsonian; cations containing agents such as aluminum, calcium, bismuth and iron salts; sucralfate, calcium channel blockers, diuretics, anti-inflammatories, opioids substances, clonidine, ganglion blockers and mixtures thereof.

15. Process, according to claims 8 and 9, characterized by the fact that the lipotropic agents are selected from the group consisting of methionine, choline bitartrate and mixtures thereof.

16. Process, according to claims 8 and 9, characterized by the fact that the auxiliary granulation solution comprises polividone.

17. Process, according to claims 8 and 9, characterized by the fact that the lubricant and/or adsorbent are selected from the group comprising magnesium stearate, sodium croscarmellose, silicon dioxide and mixtures thereof.

18. Process, according to claims 8 and 9, characterized by the fact that step e) comprises diluents selected from the group comprising Microcrystalline Cellulose, Corn Starch and mixtures thereof.

19. Process, according to claims 8 and 9, characterized by the fact that step e) comprises tabletting excipients selected from the group comprising shellac, talc, sugar, titanium dioxide, arabic gum and mixtures thereof.

20. Process, according to claims 8 and 9, characterized by the fact that step e) comprises tabletting polishing excipients selected from the group comprising beeswax, carnauba wax and mixtures thereof.

21. Process, according to claims 8 and 9, characterized by the fact that step e) comprises colorants selected from the group comprising Ponceau Red.