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(54) Title: FORMULATIONS COMPRISING HERBAL EXTRACTS

(57) Abstract: The present invention relates to formulations comprising pelargonium sidoides extract and propolis extract for providing treatment in various respiratory diseases such as cold, cough, allergic asthma, seasonal allergic rhinitis, bronchitis, pharyngitis, laryngitis and pneumonitis.



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FORMULATIONS COMPRISING HERBAL EXTRACTS

Technical Field

The present invention relates to formulations comprising pelargonium sidoides extract and propolis extract for providing treatment in various respiratory diseases such as cold, cough, allergic asthma, seasonal allergic rhinitis, bronchitis, pharyngitis, laryngitis and pneumonitis.

Background of Invention

In recent years, the use of various herbs and/or herbal medical products for the prevention and treatment of diseases and alleviating the effects thereof have been gradually increasing in all societies. Throughout the human history, there have been and still are attempts for treating many diseases (diabetes, jaundice, dyspnea, etc.) by using some herbs. According to the records of the World Health Organization (WHO), a large proportion of the world's population (70-80%) make use of herbs for therapeutic or prophylactic purposes. Additionally, around 25% of prescription drugs in developed countries are composed of plant-based active agents (vinblastine, reserpine, quinine, aspirin, etc.).

Particularly following the end of the 1990s, the discovery of new areas of use for medical and aromatic herbs and the increasing demand for natural products have increased the use potential thereof day by day.

Herbal medical products have long been in use for the treatment or prophylaxis of respiratory diseases. In the treatment or prophylaxis of these diseases which are typically caused by viruses, bacteria, and/or fungi, it is quite significant both to eradicate these harmful organisms and to boost the immune system of the affected individual. This is because the immune system is comprised of processes providing protection against diseases, as well as recognizing and eliminating the pathogenic and tumor cells in a living being. The system scans the organism against any kind of foreign substances, entering or contacting the former, from viruses to parasitic worms of a wide variety, and distinguishes them from the organism's own healthy cells and tissues. The immune system can even distinguish substances with very similar features from each other to such an extent that even proteins having a different amino acid can be distinguished from

the equivalents thereof. The function of the immune system is primarily to prevent harmful foreign substances from entering the respective organism, or upon entry, to retain the substances at the place of entry, or to prevent or delay their spreading therein.

Propolis is one of the most important bee products. Besides its antibacterial, antifungal, antiviral features, a great number of beneficial biological activities such as anti-inflammatory, anti-ulcer, local anesthetic, anti-tumor and immunity stimulant properties popularizes its usage in medicine, apitherapy, health nutrition and biocosmetic fields. It comprises 150 chemical compounds, more than 20 mineral substances, beeswax, resin and pollen. In chemical terms, propolis comprises a wide variety of extremely complex and potent terpenes, benzoic acids, caffeic acids, cinnamic acids, and phenolic acids. It has a high flavonoid content.

Propolis is one of the most powerful antibiotics found in nature. It is rich in terms of amino acids and trace metals, has a very high vitamin content and contains at least 38 valuable bioflavonoids. It is an invaluable antioxidant based on its high bioflavonoid content. It was demonstrated to inactivate at least 21 bacteria species, 9 fungi species, 3 protozoa (including giardia), and a wide spectrum of viruses.

In the studies, many advantages of propolis for health have been demonstrated. Some examples of these studies are: 1) A clinical study conducted in Spain in 1988 on 138 individuals has shown that the usage of a propolis based supplement is as effective as the usage of antiprotozoal drug tinidazole which is extensively used in the treatment of infections caused by giardiasis parasite. 2) A study published in Nutrition and Cancer in 2003 has shown that propolis has revitalized apoptosis and provided the tissue decomposition of the lung cancer tumors in mouse. 3) According to National Institutes of Health, propolis may be used as an effective anti-inflammatory agent against aphtha and other gingiva wounds and peptic ulcer. 4) Blue Shield Complementary and Alternative Health has reported that propolis is two times more effective than acyclovir which is the conventional anti-viral drug in herpes treatment. 5) According to a study published in American Journal of Biochemistry and Biotechnology on February 2004, propolis kills the human breast cancer cells called MCF-7. 13% of the cancer cells of the participants were killed only within 24 hours following the administration of propolis extract.

Pelargonium sidoides (African Geranium, Umckaloabo) is a plant species widely used in the treatment and prevention of, or in the alleviation and/or elimination of the symptoms of cold and respiratory tract disease (pharyngitis, sinusitis, acute bronchitis, tonsillitis). It

was determined to be effective in increasing the generation of natural killer cells and tumor necrosis factor alpha, and to enhance the release of interferon beta. Pelargonium sidoides has antiviral properties strengthening the immune system. It further has both antibacterial effects and antioxidative properties against some bacteria. Apart from that, it was also reported to boost the immune system of the respective organism and to have expectorant action by increasing the ciliary beat frequency of respiratory epithelial cells. In a multicenter study conducted by the Pneumology Department of a German University Hospital (2000) on acute bronchitis patients, including adults, children, and infants, it was determined that an extract of the roots of Pelargonium sidoides reduced the severity of the symptoms after 7 days treatment from 6.3 to 0.9 according to the average bronchitis severity score. A study published in "Acta Paediatrica" in April 2010, showed that preparations extracted from herbal roots were much more effective in the treatment of acute bronchitis as compared to placebo. A study group of children aged 6 to 18 years, taking the herbal extracts experienced less coughing, sputum, and bed rest times versus placebo. By assessing the results of four placebo-controlled clinic trials, the researchers at the Medical Center, the University of Pittsburgh, concluded that a standardized extract of Pelargonium sidoides showed a much better performance in alleviating the bronchitis symptoms versus placebo in a 7-day treatment period.

Luo Han Guo (luohanguo) refers to the fruit of *Siraitia grosvenori*, formerly called *Momordica grosvenori*, a member of the *Curcubitaceae*. The plant is cultivated for its fruit Luo Han Guo, whose extract is nearly 300 times sweeter than sugar and has been used in China as a natural low-calorie sweetener and in traditional Chinese medicine to treat diabetes and obesity. Luo Han Guo is popularly considered a longevity aid and is used to balance heat buildup caused by internal conditions, life-forces, or external heat. It is used as an expectorant and antitussive to treat lung congestion, cough, other respiratory ailments, and sore throat. It also is used for constipation and chronic enteritis. Luo Han Guo is a low-caloric, low-glycemic food used as a natural sweetener in beverages and food.

Ginger (*Zingiber officinale*) is also called "warming herb" and used for a long time as an important medical herb. It comprises essential oils with ether comprising Zingiberene, Zingiberol, Gingerol and Shogol. The essential oils contained which are mixed with terpenoids give the special taste and scent of ginger. The bitter substances without essential oils which make the mouth feel warm are gingerol and zingeron.

Ginger has a wide area of usage. Ginger is preventive against cancer based on stopping the Epstein-barr virus activity. 6-gingerol and 6-paradol, among the active substances of ginger, are effective in stopping promyelocytic leucaemia by disturbing the DNA synthesis. It also has anti-inflammatory effect, is effective against arthritis and headache, and is bacteriostatic. It is used against nausea, spasm and fever in kids. Based on its antiseptic effect, it is used against stomach and intestine infections and even against food poisoning. It also prevents the coagulation of the blood and has blood thinning effect. It supports the cardiovascular system by making the platelets less adherent, this in turn causes a decrease in the problems of circulation system. It is appetizing and can also be used against constipation. In addition to these, it has a warming and sedative effect in cough, flu, cold and other respiratory system diseases.

Echinacea purpurea, the purple coneflower, is a plant species widely used in the prophylaxis and/or treatment of infection, cold, cough, bronchitis, flu, in the treatment of infection of the urinary system, in the treatment of the sore throat and toothache, in boosting the immune system, and externally, in the treatment of snakebite, eczema, psoriasis, acne, wounds and burns. *Echinacea purpurea* is known to have immunostimulant, anti-inflammatory, antibacterial, antiviral, antifungal, anticancer, cicatrizing activities. The compounds accounting for these activities are thought to be polysaccharides, glycoproteins, alkylamides, and caffeic acid derivatives (cichoric acid, echinacoside). *Echinacea purpurea* supports the production of interferon, thereby strengthening the defense system of the respective organism. Interferon activates the natural killer cells and induces these cells to bind to and destroy infected cells or tumor bearing cells. Interferon is effective in releasing the enzymes destroying the genetic structure of viruses and inhibiting their reproductive and spreading capabilities.

Ginseng root is harvested after a cultivation period of 6 years and this part of the plant is used for therapeutic purposes. It comprises saponins (dammaran and oleanan derivatives; ginsenosides), polyacetylene derivatives and polysaccharides. The effects of Ginseng on the body are not local, and thus, one of the benefits of Ginseng is that it strengthens the entire body and helps in balancing entire body systems. Ginseng is an antioxidant and an important immunity system improver which increases the number of immunity system cells in the body. It is useful in the treatment of bronchitis, asthma and circulation problems. According to a study conducted by American scientists, the flu risk of people who are administered 200mg ginseng root capsules twice a day reduced by 31%. In the laboratory and animal experiments, it is found that it is effective against

prostate, stomach, kidney, liver, large intestine, brain and lung cancers. In the animals with prostate cancer, it prevented the development of cancer.

Berberis vulgaris berries are edible and rich in vitamin C. Berberine is the main active alkaloid with a benzyl tetra hydroxy quinoline chemical structure which can be found in all part of berberis vulgaris especially in its fruit (barberry). It is odorless but with a bitter taste powder which is sparingly soluble in methanol, slightly soluble in ethanol and very slightly soluble in water.

Honey is the natural product processed by honeybees from flower nectars or plant secretions, by aid of their own secretions. Honey is a nutritious, sweet and healthy food, and minor components of honey include proteins (0.25–0.5%), organic acids, aminoacids, vitamins, flavonoids and water. The amount of water in honey is between 15.00% and 30.00% by weight.

Honey has been used for treatment of microbial infections since ancient times. In recent years there has been a resurgence of interest in the therapeutic efficacy of honey. While it may naturally have a long shelf life, heating and cooling the spread too many times can cause it to lose its colour and aroma. Shelf-life of honey depends on botanical origin as well as processing.

Products to be used for medical purposes have to incorporate the elements of quality, efficiency, and reliability. A product can be a "medical" product only by having these elements. In order for a product prepared from a herbal source to be a medical product, it has to be prepared from an efficient and standardized extract, to have established pharmacological, clinical outcomes and toxicological data, and have a determined stability. Therefore, it bears great significance to have a good stability for a product, produced from herbal sources, to be used in the treatment and prevention of diseases, or in the alleviation and/or elimination of the symptoms thereof.

Physical, chemical, and microbiological factors play role in the stability of medicaments or other products prepared for medical purposes. The stability issue is not dependent on a simple cause only, but emerges as a result of many factors. Factors such as the interaction of active agents contained in a product, the interaction of excipients among themselves or with active agents, pH, light, humidity, and temperature are among many elements which may influence the stability of such products.

Until recently, the researchers deemed considerable importance on the chemical stability of pharmaceutical products rather than the physical stability thereof and conducted many studies accordingly. In many instances, however, they could show how important the changes in the physical structures of products are for the product quality, and for the durability of the technologic, microbiologic, and biopharmaceutical properties thereof. Accordingly, it was shown that primarily the physical stability of a product has to be maintained in order to sustain its quality and other features thereof, and therefore ensuring the physical stability during the development of pharmaceutical products is as important as, or sometimes more important than ensuring the chemical stability thereof.

Additionally, the physical properties taken into account in the evaluation of the physical stability of a product, particularly the taste, scent, color, clarity, uniformity, etc., also considerably influence the patient compliance. For this reason, when a novel formulation is developed, besides aiming a formulation of good physical stability, the physical properties of this formulation should be made ideal to provide high patient compliance.

However, it is quite difficult to provide the above described conditions in the formulations comprising herbal substances. Due to some characteristic chemical, biological and physical properties of the herbal substances used in the formulation, some problems are encountered in obtaining a formulation comprising said substances as well as having a good physical stability and ideal physical properties in terms of patient compliance.

The physical properties and the physical stability of a formulation are influenced directly from the characteristic properties of herbal agents contained therein. Some aspects of herbal agents contained in a formulation, such as having a bad taste, a bad scent, a bad color and similar physical properties, becoming easily oxidized, and providing a suitable medium for the reproduction of microorganisms negatively influence the physical properties and physical stability of that formulation. Additionally, in case a formulation comprises a combination of herbal agents, a correct selection of the herbal agents bears great importance, since more than one herbal agent present in the same formulation are capable to mutually affect their respective properties.

Even if there are formulations comprising herbal extracts prior art, it would be desirable to provide a new formulation, as well as a process for the preparation of this formulation, comprising combinations of herbal agents, being capable to retain the physical stability for a long time, and having ideal physical properties in terms of patient compliance for the treatment of respiratory diseases.

In detail, there is a need in the state of art for a formulation comprising pelargonium sidoides extract and propolis extract, and having ideal physical properties to ensure high patient compliance and good physical stability, as well as to a method for preparing this formulation, which is simple, cost-efficient and time-saving.

5 **Object of the Invention**

The main object of the present invention is to obtain formulations which have improved physical stability, comprising pelargonium sidoides extract and propolis extract.

10 Another object of the present invention is to provide formulations with a significantly improved stability, as well as the excellent long-term stability.

Another object of the present invention is to provide formulations for providing treatment in various respiratory diseases such as cold, cough, allergic asthma, seasonal allergic
15 rhinitis, bronchitis, pharyngitis, laryngitis and pneumonitis.

Another object of the present invention is to provide formulations which have increased quality, reliability, and shelf life as a result of an improved physical stability.

20 Another object of the present invention is to provide formulations comprising pelargonium sidoides extract and propolis extract, which both maintains the physical stability and has improved physical properties as a result of using suitable excipients.

Yet another object of the present invention is to develop formulations which are capable
25 of providing an easy administration accompanied by an increased patient compliance and convenience.

A further object of the present invention is to provide a simple, cost-efficient, and time-saving process for preparing formulations comprising pelargonium sidoides extract and
30 propolis extract.

A further object of the present invention is to provide an improved oral film formulation of pelargonium sidoides extract and propolis extract.

A further object of the present invention is to provide stable oral film dosage forms by making use of convenient excipients, which do not stick to each other, and have a taste which is not unpleasant, comprising pelargonium sidoides extract and propolis extract.

5 **Detailed Description of Invention**

In order to achieve the aforementioned objects, the present invention discloses a novel, stable, formulations of extracts of pelargonium sidoides and propolis.

10 The maintenance of the physical stability of a pharmaceutical product can be ensured if no change occurs in the physical structure of that product. Therefore, whether the physical stability is maintained or not is assessed by determining changes in various physical properties of the product during formulation development process. Properties such as the color, scent, taste, pH, clarity, viscosity, homogeneity, density which are
15 among the physical properties of a pharmaceutical are the basic physical properties playing role in the assessment of the physical stability thereof.

Surprisingly, in the physical stability studies conducted during development of a herbal formulation comprising pelargonium sidoides extract for medical purposes, it is found that
20 in the event of adding another substance, propolis extract, into the formulation, physical stability of the product is improved. Furthermore, owing to therapeutic properties of propolis, the efficacy of the formulation increases.

A formulation according to the present invention, comprises pelargonium sidoides extract
25 and propolis extract.

In one embodiment, the amount of pelargonium sidoides extract in the formulation is between 0.10% and 1.00% by weight of the total formulation.

30 In one preferred embodiment, the amount of pelargonium sidoides extract in the formulation is between 0.20% and 0.80% by weight of the total formulation.

In one embodiment, the amount of propolis extract in the formulation is between 0.01% and 1.00% by weight of total formulation.

35 In one preferred embodiment, the amount of propolis extract in the formulation is between 0.01% and 0.06% by weight of total formulation.

In another embodiment, the weight ratio of pelargonium sidoides extract to propolis extract is more than 10.00, preferably between 10.00 and 15.00. This specific ratio helps ensure physical stability.

5

In one embodiment, the formulation comprises at least one additional herbal extract which is selected from a group comprising berberis vulgaris, siraitia grosvenorii, panax ginseng, glycyrrhiza glabra, echinacea purpurea, tilia, zingiber officinale, citrus junos, licorice, heder helix, ginkgo biloba, turmeric, capsicum, sage, rosemary, maca, rhodiola or combinations thereof.

10

According to one embodiment, the additional herbal extract is berberis vulgaris.

According to this embodiment, the amount of berberis vulgaris in the formulation is between 0.01% and 1.00% by weight of total formulation. Preferably the amount of berberis vulgaris in the formulation is between 0.01% and 0.20% by weight of total formulation.

15

According to one embodiment, the additional herbal extract is siraitia grosvenorii.

According to this embodiment, the amount of siraitia grosvenorii in the formulation is between 0.01% and 10.00% by weight of total formulation. Preferably the amount of siraitia grosvenorii in the formulation is between 0.05% and 5.00% by weight of total formulation.

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According to one embodiment, the additional herbal extract is panax ginseng.

According to this embodiment, the amount of panax ginseng in the formulation is between 0.05% and 1.00% by weight of total formulation. Preferably the amount of panax ginseng in the formulation is between 0.09% and 0.50% by weight of total formulation.

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According to one embodiment, the additional herbal extract is glycyrrhiza glabra.

According to this embodiment, the amount of glycyrrhiza glabra in the formulation is between 0.05% and 1.00% by weight of total formulation. Preferably the amount of glycyrrhiza glabra in the formulation is between 0.09% and 0.50% by weight of total formulation.

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According to one embodiment, the additional herbal extract is echinacea purpurea.

According to this embodiment, the amount of echinacea purpurea in the formulation is between 0.05% and 1.00% by weight of total formulation. Preferably the amount of echinacea purpurea in the formulation is between 0.09% and 0.50% by weight of total formulation.

According to one embodiment, the additional herbal extract is tilia.

According to this embodiment, the amount of tilia in the formulation is between 0.05% and 1.00% by weight of total formulation. Preferably the amount of tilia in the formulation is between 0.09% and 0.40% by weight of total formulation.

According to one embodiment, the additional herbal extract is zingiber officinale.

According to this embodiment, the amount of zingiber officinale in the formulation is between 0.01% and 1.00% by weight of total formulation. Preferably the amount of zingiber officinale in the formulation is between 0.01% and 0.40% by weight of total formulation.

According to one embodiment, the formulation further comprises zinc sulphate monohydrate.

According to this embodiment, the amount of zinc sulphate monohydrate in the formulation is between 0.10% and 1.00% by weight of total formulation. Preferably the amount of zinc sulphate monohydrate in the formulation is between 0.10% and 0.50% by weight of total formulation.

According to one embodiment, the formulation further comprises at least one cooling agent which is selected from a group comprising menthol, thymol or mixtures thereof.

When menthol or thymol or mixtures thereof is selected as the cooling agent, the therapeutic effect of the formulation is supported by the antiseptic and antibacterial properties of menthol and thymol.

In one embodiment, the amount of menthol in the formulation is between 0.00% and 3.00%, preferably between 0.01% and 3.00%, and the amount of thymol in the formulation is between 0.00% and 3.00%, preferably between 0.01% and 3.00% by weight of total formulation.

5

In one embodiment, the formulation further comprises at least one pharmaceutically excipient which is selected from a group comprising sweeteners, flavouring agents or mixtures thereof.

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Suitable sweeteners are selected from a group comprising honey, xylose, ribose, glucose, sucrose, maltose, stevioside, fructose, thaumatin, mogroside, sucralose, erythritol, inulin, sodium saccharin, calcium saccharin, cyclamate salts, acesulfame-K, aspartame, sorbitol, mannitol, isomalt, maltitol, neotame, sucralose, alitame or mixtures thereof.

15

In one preferred embodiment, the sweetener is honey.

According to this embodiment, the amount of honey in the formulation is between 0.00-80.00%, preferably between 5.00% and 80.00% by weight of total formulation.

20

The selection of the sweetener has surprisingly provided the oral film dosage forms which do not stick to each other and have a taste which is not unpleasant.

According to this embodiment, honey is in natural form.

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Using natural honey also increases the stability of the formulation due to its protective properties and long shelf-life.

30

Suitable flavouring agents are selected from a group comprising eucalyptol, menthol, peppermint, cinnamon, chocolate, vanilla, cocoa, coffee, chocolate, citrus, and fruit essences such as apple, raspberry, pineapple, cherry, orange, strawberry, grape, tutti frutti or mixtures thereof.

In one preferred embodiment, the flavouring agent is eucalyptol.

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According to this preferred embodiment, the amount of eucalyptol in the formulation is between 0.05% and 1.00% by weight of total formulation.

Since eucalyptol has antibacterial and anticeptic qualities, it has been shown to protect against microbial growth that can promote a host of different symptoms and diseases in the body. In this invention, one important reason that the inventors preferably use eucalyptol is that it creates a cooling and refreshing effect.

In one embodiment, the formulation comprises;

- a. pelargonium sidoides extract 0.1% to 1.00%
- b. propolis extract 0.01% to 1.00%
- c. berberis vulgaris extract
- d. zinc sulphate monohydrate
- e. glycyrrhiza glabra extract
- f. echinacea purpurea extract
- g. panax ginseng extract
- h. tilia extract
- i. eucalyptol
- j. zingiber officinale extract
- k. luo han guo extract

In one embodiment, the formulation is administered by oral, parenteral, ocular, nasal, buccal, sublingual or topical route.

In one preferred embodiment, the formulation is administered by oral route.

According to these embodiments, the formulation is in the form of oral film, lozenges, tablets, effervescent tablets, effervescent sachets, orally disintegrating tablets, sublingual tablets, buccal tablets, capsules or syrup.

In one preferred embodiment, the formulation is in the form of an oral film.

Among the delivery routes, the oral route is the most acceptable from patient compliance aspects. One such relatively new dosage form is the oralstrip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity or sublingual use.

The oral or sublingual or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass

hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.

However, not all drugs can be incorporated into this dosage form and no oral film formulation was disclosed previously which comprises herbal extracts.

Various formulations and methods for preparing oral film formulations have already been known. However, concerning oral administration, oral film formulations have become an issue with increasing importance in terms of patient compliance as compared to conventional solid dosage forms such as capsules and tablets. This issue is more important in terms of patients having difficulty in swallowing. Additionally, concerning many drugs, the swallowing of the same usually necessitates fluids to increase the gastric volume and increases the likelihood of nausea and vomiting. Probably the greatest advantage of an oral film dosage form is that the solid dosage forms rapidly dissolve or disintegrate in the oral cavity so that a solution or suspension forms therein without having to take any liquid. Additionally, the oral films having a low layer thickness and therefore a large surface area rapidly disintegrate in the mouth mucosa. Thus, it will suffice to administer the dosage form briefly before the patient will need it. In addition to these, the oral film dosage forms are more easily used and carried. They are preferred by patients since they do not require carrying any blister packs.

For these reasons, the oral film dosage forms are one of the advantageous ways for administering herbal extracts and provide a better patient compliance along with the recommended pharmaceutical therapies.

The oral film formulations provide for a more rapid absorption of the herbal extracts in the buccal oral or sublingual mucosa, and this may reduce the first pass effect and thus the efficiency of the extracts is enhanced. Since this dosage form stays away from the hepatic first-pass metabolism, it increases the clinic effects of active agents by increasing the bioavailability and decreasing the side-effects thereof.

Developing an oral film composition is known to be difficult for several different reasons. First, the oral film formulations comprising herbal extracts may be problematic based on their unpleasant taste. Moreover, these compositions should be flexible and not too rigid. These compositions are quite susceptible to the moisture and the films are prone to adhere to each other. As a result of this, they may show some stability problems.

The film obtained should be tough enough to ensure not to be damaged while handling or during transportation. The robustness of the strip depends on the type of polymer and its amount in the formulation. On the other hand, fast dissolving strip dosage form should have the property to disintegrate in seconds when placed in mouth and deliver the drug to the oral cavity instantaneously.

In order to fulfill all these requirements described above, a special formulation is needed and therefore the excipients should be selected carefully.

Therefore, the oral film formulation of pelargonium sidoides extract and propolis extract and a process for preparing this formulation are required.

In one embodiment, the formulation further comprises at least one pharmaceutically acceptable excipient which is selected from a group comprising sweeteners, flavouring agents, film forming agents, plasticizers, surfactants or mixtures thereof.

In the oral film formulation according to the present invention, suitable amounts of suitable excipients have to be used that do not adhere to each other during storage and therefore are stable throughout the shelf life, and prevent the bitter taste.

Suitable sweeteners are selected from a group comprising honey, xylose, ribose, glucose, sucrose, maltose, stevioside, fructose, thaumatin, mogroside, sucralose, erythritol, inulin, sodium saccharin, calcium saccharin, cyclamate salts, acesulfame-K, aspartame, sorbitol, mannitol, isomalt, maltitol, neotame, sucralose, alitame or mixtures thereof.

In one preferred embodiment, the sweetener is honey.

According to this embodiment, the amount of honey in the formulation is between 5.00% and 80.00% by weight of total formulation.

The selection of the sweetener has surprisingly provided the oral film dosage forms which do not stick to each other and have a taste which is not unpleasant.

According to this embodiment, honey is in natural form.

Using natural honey also increases the stability of the formulation due to its protective properties and long shelf-life.

Suitable flavouring agents are selected from a group comprising eucalyptol, menthol, peppermint, cinnamon, chocolate, vanilla, cocoa, coffee, chocolate, citrus, and fruit essences such as apple, raspberry, pineapple, cherry, orange, strawberry, grape, tutti frutti or mixtures thereof.

In one preferred embodiment, the flavouring agent is eucalyptol.

According to this preferred embodiment, the amount of eucalyptol in the formulation is between 0.05% and 1.00% by weight of total formulation.

An ideal oral formulation should give a pleasing mouth feel. When eucalyptol is used as the flavouring agent, it is observed that it shows a supporting effect for said formulation due to the refreshing, cooling and smoothening effect of scent and the patients administered with said formulation feels instant relief and alleviation of symptoms, thus, it helped them feel better within a shorter period of time.

Suitable film forming agents are selected from a group comprising pullulan, guar gum, methyl cellulose, polyvinyl pyrrolidone, carboxymethylcellulose, pectin, gelatin, sodium alginate, hydroxypropyl cellulose, polyvinyl alcohol, maltodextrin, microcrystalline cellulose, amino alkyl methacrylate copolymers, sodium carboxymethyl cellulose, polyethylene oxide, modified starches, hydroxyethyl cellulose, locust bean gum, rosin, chitosan, carragennan, xanthan gum or mixtures thereof.

In one preferred embodiment, the film forming agents are selected from pullulan, guar gum or mixtures thereof.

In one preferred embodiment, the film forming agents are pullulan and guar gum.

Pullulan is a natural polymer obtained from non-animal origin and does not require chemical modification. This polymer provides highly clear and homogenous films. It has low oxygen permeability and low water content which makes it most suitable for production of oral films in this invention.

In one embodiment, the amount of pullulan in the formulation is between 0.50% and 50.00% by weight of total formulation.

In one embodiment, the amount of guar gum in the formulation is between 0.05% and 25.00% by weight of total formulation.

Suitable plasticizers are selected from a group comprising glycerin, monopropylene glycol, polyethylene glycol, dibutyl phthalate, triacetin, castor oil, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, tributyl citrate, triethyl citrate, acetyl citrate or mixtures thereof.

In one preferred embodiment, the plasticizers are selected from glycerin, monopropylene glycol or mixtures thereof.

In one preferred embodiment, the plasticizers are glycerin and monopropylene glycol.

According to this preferred embodiment, the amount of glycerin in the formulation is between 1.00% and 35.00%, the amount of monopropylene glycol is between 1.00% and 35.00% by weight of total formulation.

Plasticizer is a vital ingredient of the oral film formulation. It helps to improve the flexibility of the strip and reduces the brittleness of the film. Using glycerin and monopropylene glycol as plasticizers, significantly improves the film properties by reducing the glass transition temperature of the polymer.

It has been found that the use of a plasticizer in the oral film formulations comprising pelargonium siloides extract and propolis extract has a positive effect on the oral film dosage forms in that they can be stored in a storage container without sticking to each other.

Suitable surfactants are selected from a group comprising polysorbate, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, poloxamer or mixtures thereof.

In one preferred embodiment, the surfactant is polysorbate.

According to this preferred embodiment, the amount of polysorbate in the formulation is between 0.05% and 10.00% by weight of total formulation.

Surfactants act as solubilizing or wetting or dispersing agent in formulation so that the film is getting dissolved within seconds and release active agent quickly.

According to another object of the present invention, the thickness of the oral films obtained influences the flexibility and the friability of the oral films. Accordingly, the thickness of the oral film is between 0.001 and 3 mm, preferably between 0.003 and 2 mm, and more preferably between 0.004 and 1 mm.

In another aspect, the present invention shows the possibility of providing significant influences on the disintegration time of the oral film dosage form by modifying the size and the shape thereof. In general terms, the disintegration process of an oral film dosage form occurs after the entire surface of an oral film dosage form gets wet by means of capillary effect. Additionally, all shapes maximizing the contact surface area with saliva may provide a significant reduction in the disintegration time.

A preferred shape of the oral film formulation according to the present invention is a disk, circle, ellipse, triangle, square, polygon, sphere, bar, etc.

A formulation according to the present invention may be produced by means of solvent casting method, semi-solid casting method, solid dispersion extrusion method, rolling method, hot melt extrusion method.

In the solvent casting method, polymer(s) in a formulation are dissolved in a suitable solvent to obtain a solution. The active agents and other excipients in the formulation are dissolved in a suitable solvent to obtain another solution or dispersion. Then both solutions are mixed and entrapped air is removed under vacuum. The resulting solution is cast to form oral film. Then the film is dried and cut into a desired size and shape.

In the semi-solid casting method, separate solutions of the water-soluble polymer and the acidic polymers, e.g. cellulose acetate phthalate, are prepared in suitable solvents. Both these solutions are mixed and then the other excipients and the active agents are added to this mixture. The resulting mixture is coated onto unprocessed cast oral film. Then the film is dried, and cut into a desired size and shape.

In the solid dispersion extrusion method, a solid dispersion of the active agent is prepared together with other materials in the formulation and then processed in a hot melt extrusion

device. The resulting product is turned into the oral films. Then the film is cooled and cut into a desired size and shape.

In the rolling method, the solutions of the active agents and other excipients are prepared in the suitable solvents. Then these solutions are rolled onto a substrate to give oral film. Then the film is dried by means of a roller and brought into a desired shape and size.

In the hot melt extrusion method, the active agents and the polymer are mixed together. Other excipients are added to the mixture and the resulting mixture is stirred. Then, it is taken to a hot melt extrusion device and is subjected to the heat treatment. The resulting product is turned into oral film. Then the film is dried and cut into a desired size and shape.

In one embodiment, the formulation which is in the form of an oral film, comprises;

- a. pelargonium sidoides extract 0.10-1.00%
- b. propolis extract 0.01-1.00%
- c. berberis vulgaris extract 0.01-1.00%
- d. zinc sulphate monohydrate 0.10-1.00%
- e. glycyrrhiza glabra extract 0.05-1.00%
- f. echinacea purpurea extract 0.05-1.00%
- g. panax ginseng extract 0.05-1.00%
- h. tilia extract 0.05-1.00%
- i. eucalyptol 0.05-1.00%
- j. zingiber officinale extract 0.01-1.00%
- k. luo han guo extract 0.01-10.00%
- l. pullulan 0.50-50.00%
- m. guar gum 0.05-25.00%
- n. glycerin 1.00-35.00%
- o. monopropylene glycol 1.00-35.00%
- p. polysorbate 0.05-10.00%
- q. honey 0.00-80.00% (optionally)
- r. menthol 0.00-3.00% (optionally)
- s. thymol 0.00-3.00% (optionally)

The present invention is described in the following examples in more details. These examples are not limiting the scope of the present invention and should be considered under the light of the foregoing detailed disclosure.

5 Example 1: Oral film

Ingredients	% Amount
Pelargonium sidoides extract	0.10-1.00
Propolis extract	0.01-1.00
Zinc sulphate monohydrate	0.10-1.00
Glycyrrhiza glabra extract	0.05-1.00
Echinacea purpurea extract	0.05-1.00
Panax ginseng extract	0.05-1.00
Tilia extract	0.05-1.00
Eucalyptol	0.05-1.00
Zingiber officinale extract	0.01-1.00
Berberis vulgaris extract	0.01-1.00
Luo han guo extract	0.01-10.00
Honey	5.00-80.00
Pullulan	0.50-50.00
Guar Gum	0.05-25.00
Glycerin	1.00-35.00
Monopropylene glycol	1.00-35.00
Polysorbate	0.05-10.00
water*	q.s

The formulation mentioned above is prepared by following these steps:

- a. dissolving pullulan and guar gum in appropriate amount of water to form homogenous viscous solution.
- 10 b. mixing pelargonium sidoides extract, zinc sulphate monohydrate, glycyrrhiza glabra extract, echinacea purpurea extract, panax ginseng extract, tilia extract, eucalyptol, zingiber officinale extract, propolis extract, berberis vulgaris extract, luo han guo extract and honey to form an active mixture
- c. mixing glycerin, monopropylene glycol, polysorbate and water until homogeneous to
15 form emollient solution
- d. mixing emollient solution and active mixture and then mixing with viscous solution.

- e. removing the entrapped air from the viscous mixture by vacuum.
- f. coating on a non-treated casting film, sending to aeration-drying oven, subsequently winding onto roll stock and cutting into desired shapes.

5 Example 2: Oral film

Ingredients	% Amount
Pelargonium sidoides extract	0.10-1.00
Propolis extract	0.01-1.00
Zinc sulphate monohydrate	0.10-1.00
Glycyrrhiza glabra extract	0.05-1.00
Echinacea purpurea extract	0.05-1.00
Panax ginseng extract	0.05-1.00
Tilia extract	0.05-1.00
Eucalyptol	0.05-1.00
Zingiber officinale extract	0.01-1.00
Berberis vulgaris extract	0.01-1.00
Luo han guo extract	0.01-10.00
Honey	5.00-80.00
Menthol	0.01-3.00
Thymol	0.01-3.00
Pullulan	0.50-50.00
Guar gum	0.05-25.00
Glycerin	1.00-35.00
Monopropylene glycol	1.00-35.00
Polysorbate	0.05-10.00
water*	q.s

The formulation mentioned above is prepared by following these steps:

- a. dissolving pullulan and guar gum in appropriate amount of water to form homogenous viscous solution.
- b. Mixing pelargonium sidoides extract, zinc sulphate monohydrate, glycyrrhiza glabra extract, echinacea purpurea extract, panax ginseng extract, tilia extract, eucalyptol, zingiber officinale extract, propolis extract, berberis vulgaris extract, loo han guo extract and honey to form an active mixture

- c. mixing glycerin, monopropylene glycol, polysorbate and water until homogeneous to form emollient solution
- d. dissolve menthol and thymol in the emollient solution.
- e. mixing emollient solution and active mixture and then mixing with viscous solution.
- 5 f. removing the entrapped air from the viscous mixture by vacuum.
- g. coating on a non-treated casting film, sending to aeration-drying oven, subsequently winding onto roll stock and cutting into desired shapes.

Example 3: Oral film

Ingredients	% Amount
Pelargonium sidoides extract	0.10-1.00
Propolis extract	0.01-1.00
Zinc sulphate monohydrate	0.10-1.00
Glycyrrhiza glabra extract	0.05-1.00
Echinacea purpurea extract	0.05-1.00
Panax ginseng extract	0.05-1.00
Tilia extract	0.05-1.00
Eucalyptol	0.05-1.00
Zingiber officinale extract	0.01-1.00
Berberis vulgaris extract	0.01-1.00
Luo han guo extract	0.01-10.00
Menthol	0.01-3.00
Thymol	0.01-3.00
Pullulan	0.50-50.00
Guar Gum	0.05-25.00
Glycerin	1.00-35.00
Monopropylene glycol	1.00-35.00
Polysorbate	0.05-10.00
water*	q.s

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The formulation mentioned above is prepared by following these steps:

- a. dissolving pullulan and guar gum in appropriate amount of water to form homogenous viscous solution.
- 15 b. Mixing pelargonium sidoides extract, zinc sulphate monohydrate, glycyrrhiza glabra extract, echinacea purpurea extract, panax ginseng extract, tilia extract, eucalyptol,

zingiber officinale extract, propolis extract, berberis vulgaris extract and luo han guo extract to form an active mixture

- c. mixing glycerin, monopropylene glycol, polysorbate and water until homogeneous to form emollient solution
- 5 d. dissolve menthol and thymol in the emollient solution.
- e. mixing emollient solution and active mixture and then mixing with viscous solution.
- f. removing the entrapped air from the viscous mixture by vacuum.
- g. coating on a non-treated casting film, sending to aeration-drying oven, subsequently winding onto roll stock and cutting into desired shapes.

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CLAIMS

1. A formulation comprising pelargonium sidoides extract and propolis extract.
- 5 2. The formulation according to claim 1, wherein the amount of pelargonium sidoides extract in the formulation is between 0.10% and 1.00% by weight of the total formulation.
- 10 3. The formulation according to claim 1, wherein the amount of propolis extract in the formulation is between 0.01% and 1.00% by weight of total formulation.
- 15 4. The formulaton according to any of the preceding claims, wherein the weight ratio of pelargonium sidoides extract to propolis extract is more than 10.00, preferably between 10.00 and 15.00.
- 20 5. The formulation according to claim 1, wherein the formulation comprising at least one additional herbal extract which is selected from a group comprising berberis vulgaris, siraitia grosvenorii, panax ginseng, glycyrrhiza glabra, echinacea purpurea, tilia, zingiber officinale, citrus junos, licorice, heder helix, ginkgo biloba, turmeric, capsicum, sage, rosemary, maca, rhodiola or combinations thereof.
- 25 6. The formulation according to claim 5, wherein said at least one additional herbal extract is berberis vulgaris.
- 30 7. The formulation according to claim 5, wherein said at least one additional herbal extract is siraitia grosvenorii.
8. The formulation according to claim 5, wherein said at least one additional herbal extract is panax ginseng.
- 35 9. The formulation according to claim 5, wherein said at least one additional herbal extract is glycyrrhiza glabra.
10. The formulation according to claim 5, wherein said at least one additional herbal extract is echinacea purpurea.
11. The formulation according to claim 5, wherein said at least one additional herbal extract is tilia.

12. The formulation according to claim 5, wherein said at least one additional herbal extract is zingiber officinale.
13. The formulation according to any of the preceding claims, wherein the formulation further comprising zinc sulphate monohydrate.
14. The formulation according to claim 1, wherein the formulation further comprising at least one cooling agent which is selected from a group comprising menthol, thymol or mixtures thereof.
15. The formulation according to claim 1, wherein the formulation further comprising at least one pharmaceutically excipient which is selected from a group comprising sweeteners, flavouring agents or mixtures thereof.
16. The formulation according to any of the preceding claims, wherein the formulation comprising;
- a) pelargonium sidoides extract 0.10% to 1.00%
 - b) propolis extract 0.01% to 1.00%
 - c) berberis vulgaris extract
 - d) zinc sulphate monohydrate
 - e) glycyrrhiza glabra extract
 - f) echinacea purpurea extract
 - g) panax ginseng extract
 - h) tilia extract
 - i) eucalyptol
 - j) zingiber officinale extract
 - k) luohanguo extract
17. The formulation according to claim 1, wherein the formulation is in the form of oral film, lozenges, tablets, effervescent tablets, effervescent sachets, orally disintegrating tablets, sublingual tablets, buccal tablets, capsules or syrup.
18. The formulation according to claim 17, wherein the formulation is in the form of an oral film.
19. The oral film formulation according to claim 18, further comprising at least one pharmaceutically acceptable excipient which is selected from a group comprising sweeteners, flavouring agents, film forming agents, plasticizers, surfactants or mixtures thereof.

- 5 20. The formulation according to claim 15 or 19, wherein the sweetener or a mixture of sweeteners is selected from a group comprising honey, xylose, ribose, glucose, sucrose, maltose, stevioside, fructose, thaumatin, mogroside, sucralose, erythritol, inulin, sodium saccharin, calcium saccharin, cyclamate salts, acesulfame-K aspartame, sorbitol, mannitol, isomalt, maltitol, neotame, sucralose, alitame or mixtures thereof.
- 10 21. The formulation according to claim 15 or 19, wherein the flavouring agent is selected from a group comprising eucalyptol, menthol, peppermint, cinnamon, chocolate, vanilla, cocoa, coffee, chocolate, citrus, and fruit essences such as apple, raspberry, pineapple, cherry, orange, strawberry, grape, tutti frutti or mixtures thereof.
- 15 22. The formulation according to claim 21, wherein the flavouring agent is eucalyptol.
- 20 23. The formulation according to claim 19, wherein said at least one film forming agent is selected from a group comprising pullulan, guar gum, methyl cellulose, polyvinyl pyrrolidone, carboxymethylcellulose, pectin, gelatin, sodium alginate, hydroxypropyl cellulose, polyvinyl alcohol, maltodextrin, microcrystalline cellulose, amino alkyl methacrylate copolymers, sodium carboxymethyl cellulose, polyethylene oxide, modified starches, hydroxyethyl cellulose, locust bean gum, rosin, chitosan, carragennan, xanthan gum or mixtures thereof.
- 25 24. The formulation according to claim 19, wherein said at least one plasticizer is selected from a group comprising glycerin, monopropylene glycol, polyethylene glycol, dibutyl phthalate, triacetin, castor oil, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, tributyl citrate, triethyl citrate, acetyl citrate or mixtures thereof.
- 30 25. The formulation according to claim 19, wherein said at least one surfactant is selected from a group comprising polysorbate, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, poloxamer or mixtures thereof.
- 35 26. The formulation according to claim 18, wherein the thickness of the oral film is between 0.001 and 3 mm, preferably between 0.003 and 2 mm, and more preferably between 0.004 and 1 mm.

27. The formulation according to claim 18, wherein the shape of the oral film is a disk, circle, ellipse, triangle, square, polygon, sphere, or bar.

28. The formulation according to any of the preceding claims, wherein the formulation which is in the form of an oral film, comprising;

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a. pelargonium sidoides extract 0.10-1.00%

b. propolis extract 0.01-1.00%

c. berberis vulgaris extract 0.01-1.00%

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d. zinc sulphate monohydrate 0.10-1.00%

e. glycyrrhiza glabra extract 0.05-1.00%

f. echinacea purpurea extract 0.05-1.00%

g. panax ginseng extract 0.05-1.00%

h. tilia extract 0.05-1.00%

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i. eucalyptol 0.05-1.00%

j. zingiber officinale extract 0.01-1.00%

k. luohan guo extract 0.01-10.00%

l. pullulan 0.50-50.00%

m. guar gum 0.05-25.00%

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n. glycerin 1.00-35.00%

o. monopropylene glycol 1.00-35.00%

p. polysorbate 0.05-10.00%

q. honey 0.00-80.00%

r. menthol 0.00-3.00%

25

s. thymol 0.00-3.00%