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(54) **Title:** AN AQUEOUS MUCOADHESIVE AND BIOADHESIVE COMPOSITION FOR THE TREATMENT

(57) **Abstract:** The present invention relates to an aqueous mucoadhesive and bioadhesive composition for the treatment of mucosal diseases, and the use of these compositions to coat mucocutaneous surfaces, such as those in the oral cavity, nasal cavity, gastrointestinal and respiratory tracts, eye, vagina, and bladder, etc. to prevent and/or treat mucosal diseases and disorders, including those which are painful, ulcerative, inflammatory, and/or erosive. The dosage forms are compositions sufficiently used to coat a wide area of the mucosal surface, but are also bioadhesive and mucoadhesive useful to provide prolonged retention on the surface of the mucosa. The compositions from liquid to solid may be used without a known pharmaceutically active compound. One or more pharmaceutically active compounds may be included in the formulation to provide additional benefit in the topical treatment of diseases, disorders and conditions of the mucosa, or for drug delivery through the mucosa to the systemic circulation.

AN AQUEOUS MUCOADHESIVE AND BIOADHESIVE COMPOSITION FOR THE TREATMENT

FIELD OF THE INVENTION

[001] The present invention relates to an aqueous mucoadhesive and bioadhesive compositions. The present invention particularly relates to the application of the aforementioned composition for the prevention and/or treatment of mucosal diseases or disorders. Further, the dosage forms of the aforementioned composition sufficiently used to coat a wide area of the mucosal surface, but are also bioadhesive and mucoadhesive useful to provide prolonged retention on the surface of the mucosa.

BACKGROUND INFORMATION

[002] Skin and Mucous membranes provide a protective layer on the surface of several body cavities, such as the oral cavity, the nasal cavity, the gastrointestinal and respiratory tracts, the vagina, and the bladder. Cells within or glands adjacent to these membranes secrete mucus, a fluid or gel primarily composed of water, lipids, inorganic salts and mucin glycoproteins, which serve to form a protective barrier to inhibit passage of harmful materials to the underlying tissue. There are several diseases, disorders and conditions of these mucosal surfaces which can result in severe pain, dryness of the buccal cavity, of the vaginal, nasal, intestinal, and eye, irritation, erythema, and/or ulceration. Examples of such diseases in the oral cavity include aphthous ulcers, bullous pemphigoid, oral lichen planus, stomatopharyngitis, in Sjogren's syndrome, oral mucositis, intestinal (nausea and vomiting, diarrhea, constipation), vaginal (e.g. vaginitis, bacterial vaginosis) and rectal mucositis, mucous membrane contact dermatitis, and inflammation and dryness of the eye (e.g. keratitis sicca, conjunctivitis, dry eye disease, uveitis) examples of diseases of the nasal mucous membrane include sinusitis and rhinitis; an example for the bladder is interstitial cystitis. Certain diseases such as Behcet syndrome, can affect the mucocutaneous membranes of several regions of the body. Many other ulcerative, moisture loss, painful, or inflammatory mucocutaneous diseases are known, including xerostomia, stomatitis (including caused by certain medications, appliances such as CPAP ma-

chines, etc.), and the like. There are also painful ulcerative disorders of mucosal surfaces which result as an adverse side-effect in certain therapies, including certain medications treating various diseases such as rheumatoid arthritis, HIV, such as dental procedures and dental/medical and non-dental/medical appliances, chemotherapy, radiation therapy or stem cell transplantation. Examples of such side-effects include mucositis, esophagitis, and radiation proctitis.

[003] The following section provides a brief description of these mucocutaneous disorders and conditions:

Aphthous Ulcers

[004] Aphthous ulcers (also known as aphthous stomatitis and canker sores) are benign open sores in the mouth, which appears as a painful white or yellow sore (ulcer) surrounded by a bright red area. Aphthous ulcers can be categorized into three groups:

[005] Minor aphthous ulcers, the most common type, which recur in crops of 1 to 5 lesions, are less than 1 cm in diameter each, and usually affect the lips, buccal mucosa, mucobuccal and mucolabial sulci, and tongue;

[006] Major aphthous ulcers, which are greater than 2 cm in diameter, begin as solitary nodules, and subsequently destroy deeper tissue, resulting in scarring that affects the movable oral mucosa and posterior mucosal surfaces; and Herpetiform ulcers, which are recurrent, multiple (10 to 100), shallow, pinpoint lesions 1 to 2 mm in diameter that may affect any part of the mucosa. The cause for any of the three types is not known, although autoimmune mechanisms are suspected.

[007] The cause can range from being well understood to unknown. There may be an inherited predisposition to their development. There may also be an immune system link. Ulcers may develop in response to mouth injury such as dental procedures or aggressive tooth cleaning. They may occur at the site of a bite when the tongue or cheek is bitten. They can also triggered by stress, dietary deficiencies (especially iron, folic acid, or vitamin B12), menstrual periods, hormonal changes, food allergies, and similar situations. They may occur with no identifiable cause. Canker sores usually appear on nonkeratinized mouth tissue including the inner surface of the cheeks

and lips, tongue, soft palate, and the base of the gums. They usually begin with a tingling or burning sensation, followed by a red spot or bump that ulcerates. Pain spontaneously decreases in 7 to 10 days, with complete healing in 1 to 3 weeks. Occasionally, a severe occurrence may be accompanied by nonspecific symptoms of illness such as fever or malaise. Recurrence is common and may continue for years (sources: WebMD, Rakel: Conn's Current Therapy 2000, 52nd ed).

[008] Aphthous ulcers are occasionally associated with macrocytic anemias or gluten-sensitive enteropathy and may become more frequent and severe in association with human immunodeficiency virus (HIV) infection (source: Goldman: Cecil Textbook of Medicine, 21st Ed.)

Behcet Syndrome

[009] Behcet's disease is a chronic multisystem disease characterized by oral and genital aphthae, arthritis, cutaneous lesions, and ocular, gastrointestinal, and neurologic manifestations. It was first described by the Turkish dermatologist Hulusi Behcet in 1937 as "recurrent oral aphthous ulcers, genital ulcers, and `hypopyon-uveitis. `" The diagnosis of Behcet's disease is based on clinical criteria as established by O'Duffy and Goldstein and the International Study Group. Complex aphthosis is the presence of almost constant, multiple oral or oral and genital aphthae in the absence of systemic manifestations. These patients must be distinguished from those with Behcet's disease.

[010] The prevalence of Behcet's disease is higher in the Middle East and Japan where it is approximately 1 in 1000. The disease is far less common in northern Europe, the United States, and the United Kingdom. The mean age of onset ranges from the mid to late 20s to the fourth decade, according to several series, with a slightly higher male to female ratio. It is relatively rare in children and the elderly. Behcet's disease is also uncommon among black Africans who, when they are affected, tend to have more mucocutaneous features. Although a definitive pattern of inheritance has not been elucidated, familial cases have been reported. Patients with complex aphthosis are probably a subset of patients with recurrent aphthous stomatitis, which is defined as the recurrence of 1 or more painful oral ulcers at intervals ranging from days to months. The prevalence of recurrent aphthosis ranges from 5%

to 66%. Onset may occur in childhood or adolescence and some patients experience a decrease in frequency with advancing age. (Source: J. V Ghate and J. L. Jorizzo, "Behcet's disease and complex aphthosis", Journal of the American Academy of Dermatology, 1999, 40(1), 1-18.)

Bullous Pemphigoid

[011] Bullous pemphigoid (BP) is an autoimmune, subepidermal blistering disease. The antigenic targets are components of the hemidesmosome; the 230-kD bullous pemphigoid antigen 1 and the 180-kD bullous pemphigoid antigen 2. It commonly affects patients in their seventh decade. About 40% of patients will experience oral involvement during the course of their disease.

[012] The mainstay of treatment for BP is systemic corticosteroids. Bullous pemphigoid is usually exquisitely sensitive to these drugs, but significant side effects in a predominantly elderly patient population limits their long-term use at therapeutic doses. Steroid-sparing agents, such as dapsone, methotrexate, and azathioprine, have been used successfully. In addition, tetracycline and niacinamide have been shown to be effective, and this combination is frequently tried first to avoid toxicity from other drugs. (Source: J. L. Popovsky and C. Camisa, "New and emerging therapies for diseases of the oral cavity", Dermatologic Clinics, 2000, 18(1), 113-125.).

Chemical and Radiation Cystitis

[013] The term `cystitis` covers a range of disorders commonly known as "painful bladder" disease in which a subject suffers bladder and/or pelvic pain and irritative voiding symptoms (urgency, frequency, nocturia, dysuria). There are a variety of known causes, which includes the damaging side-effects of radiation therapy to the lower abdomen, and cytotoxic agents and/or their metabolites as they pass through the bladder following renal clearance.

[014] Cyclophosphamide (Cytoxan), the most commonly used oxazaphosphorine, is an alkylating agent first used in the treatment of malignant tumors in Europe in 1957. Cyclophosphamide still has a role in the treatment of solid tumors and lymphomas,

as well as benign inflammatory states, Wegener's granulomatosis and rheumatoid arthritis being the most common. Other oxazaphosphorines--ifosfamide, trofosphamide, and sufosfamide--have been used since the 1970s for the treatment of solid malignancies and lymphomas. Dose-limiting toxicity with these compounds is usually urinary tract toxicity.

[015] Subsequent to treatment with these compounds, urinary symptoms including frequency, urgency, dysuria, and nocturia develop in as many as 24% of patients treated with oral.

Cytoxan

[016] Bladder pathology has been attributed to toxic metabolites of these compounds. Cyclophosphamide is broken down by hepatic microsomal cells to hydroxycyclophosphamide; then by target cells to aldophosphamide; and then to phosphoramide mustard, the active antineoplastic metabolite, and acrolein, which has no significant antitumor activity. Similarly, ifosfamide is metabolized to iphosphoramide mustard and acrolein. Urinary excretion of acrolein is believed to be the major source of urothelial toxicity. Most normal cells are able to break down the toxic metabolites and diminish their effect. Glutathione is a naturally occurring thiol that can confer such protection in most cells, but is present in low levels in urine.

[017] Oxazaphosphorine toxicity has been demonstrated in several animal models with their systemic administration and by instillation of their normal metabolic products directly into the bladder. Urine from animals given these agents, when placed in other animal bladders, will reproduce these findings, while instillation of cyclophosphamide will not. Electron microscopy suggests the initial toxic effect is disruption of the plasma membrane and cytoplasmic matrix.

[018] Bladder damage from these compounds is cumulative, and is generally dose related. "Cyclophosphamide cystitis" occurs frequently and early following intravenous (IV) therapy, especially dose-intensive regimens. Cystitis usually takes weeks to develop after oral treatment, but has been seen after as little as one dose. Fibrosis has been found in as many as 25% of children receiving high-dose cyclophospha-

mide. Severe hematuria and telangiectasia are more common in these patients. Oxazaphosphorine cystitis is potentiated by prior pelvic radiation.

[019] Cystoscopy may reveal a tumor or changes compatible with cyclophosphamide cystitis. Acutely diffuse inflammation is seen. Chronic changes include a pale bladder mucosa with telangiectasia. Areas of edema can be present with patchy hemorrhagic areas that stain with methylene blue, an indicator of mucosal injury. Biopsies reveal hyperemia, hemorrhage, edema, mucosal thinning, and ulceration of the urothelium. Necrosis of mucosa, muscle, and small arterioles and telangiectasia can be present. Atypia can be prominent, and abundant mitoses often occur. These findings are similar to those seen after radiation therapy. (Source: DeVita: Cancer: Principles and Practice of Oncology, 5th ed., Copyright.COPYRGT. 1997 Lippincott-Raven Publishers).

Erythema Multiform

[020] Erythema multiforme often affects the oral cavity and is frequently recurrent. The classic cutaneous findings are targetoid lesions symmetrically distributed over the trunk and extremities. Studies show that as many as 70% of patients develop oral lesions, which are extremely painful and often debilitating. In more than 60% of patients, the attacks followed an episode of herpes simplex virus (HSV) infection. Acyclovir or one of the newer antiviral agents can be used to suppress recurrent HSV outbreaks and to prevent recurrent erythema multiforme. The current recommendations for daily suppression of HSV are acyclovir (400 mg twice daily), famciclovir (250 mg twice daily), or alacyclovir (500 mg daily). Suppressive doses are to be used for patients who experience more than six episodes a year of HSV or HSV-induced erythema multiforme.

[021] Azathioprine (Imuran) can also be used to treat erythema multiforme. It should be used for patients who have severe mucosal involvement or in whom lesions continue to occur despite HSV suppression. In one study, 11 patients with severe disease failed to respond to acyclovir, dapsone, or antimalarials, but all cleared with azathioprine, 100 to 150 mg daily. Response was dose-dependent, and the condition relapsed when therapy was discontinued. Thalidomide has also been shown to be effective for recurrent erythema multiforme. (Source: J. L. Popovsky and C. Camisa,

"New and emerging therapies for diseases of the oral cavity", Dermatologic Clinics, 2000, 18(1), 113-125.)

Oesophagi's

[022] Esophagitis is a side-effect of the radiation therapy of the chest when the esophagus receives an unavoidable significant radiation dose.

[023] Acute side effects occurring during the course of radiotherapy are organ specific and related to the fractionation scheme, total dose, and use of sequential or concomitant chemotherapy or radiosensitizers. They typically manifest in the second to third week of treatment. A significant concern of combined therapy is the increased toxicity, which may potentially outweigh the benefit from both modalities.

[024] Most patients do not develop symptoms related to lung irradiation until the end of treatment. Some patients complain of a dry, nonproductive cough secondary to radiation effect on the trachea or bronchi. This reaction can last for several weeks after the completion of treatment. Radiation may also induce acute esophagitis during the course of therapy, which typically occurs during the second through fourth weeks of treatment, as well as shortly after completion. Chemotherapy and radiosensitizers appear to accelerate the onset and severity of symptoms. Agents such as 5-fluorouracil, doxorubicin, cisplatin, and mitomycin enhance the effect of radiation with regard to the esophagus. In general, acute esophagitis resolves shortly after the completion of radiotherapy, with few patients progressing to chronic esophagitis. Esophagitis presents with mild to severe swallowing difficulty requiring diet modification and nonnarcotic or narcotic analgesics, depending on severity. (Source: DeVita: Cancer: Principles and Practice of Oncology, 5th ed).

Interstitial Cystitis

[025] Interstitial cystitis (IC) has only recently been recognized as a major health problem. It encompasses a major portion of the "painful bladder" disease complex, which includes a large group of urologic patients with bladder and/or pelvic pain, irritative voiding symptoms (urgency, frequency, nocturia, dysuria), and negative urine

cultures. Painful bladder diseases with a well-known cause include radiation cystitis, cyclophosphamide cystitis, cystitis caused by microorganisms that are not detected by routine culture methodology, and systemic diseases affecting the bladder.

[026] One problem with defining IC is that the symptoms are in reality an exaggeration of normal sensations. Urinary frequency patterns can be related to fluid intake and age, and the signal or urge to void is considered an unpleasant or painful sensation by most persons. With no pathognomonic findings on pathologic examination, IC is truly a diagnosis of exclusion. It may have multiple causes and represent a final common reaction of the bladder to different types of insult. Thus, issues of definition are critical. To understand the current way IC is defined and how this came to be, a look back in time is helpful.

[027] In 1987 there were 43,500 (perhaps up to 90,000) diagnosed cases of IC in the United States, approximately twice the prevalence in Finland found by Oravisto 12 years earlier. More interesting, women who were diagnosed by sampled urologists as actually having IC represented only 20% of the cases presenting with symptoms (chronic painful bladder, sterile urine) that were suggestive of this disease. On the basis of these data, from 250,000 to almost 500,000 patients in the United States might have had IC in 1987, depending on the assumptions used.

[028] The median age of onset is 40 years. Up to 50% of patients experience spontaneous remissions probably unrelated to treatment with a duration ranging from 1 to 80 months (mean 8 months).Patients with IC are 10 to 12 times more likely than controls to report childhood bladder problems.

[029] The time from symptom onset to diagnosis varied from 24 months for the patients most recently diagnosed to 51 months for members of the Interstitial Cystitis Association.

[030] Taking the prevalence figure of 44,000, the IC-related incremental medical care cost in the United States was $116.6 million in 1987 and IC-related lost economic production was $311.7 million.

[031] Intravesical lavage with one of a variety of preparations remains the standard treatment against which other treatments must be measured. A mainstay of the treatment of IC is the intravesical instillation of DMSO. DMSO is a product of the

wood pulp industry and a derivative of lignin. It has exceptional solvent properties and is freely miscible with water, lipids, and organic agents. Pharnacologic properties include membrane penetration, enhanced drug absorption, anti-inflammatory properties, analgesic properties, collagen dissolution, muscle relaxation, and mast cell histamine release. In vitro effects on bladder function belie its positive effects in vivo. (Source: Walsh: Campbell's Urology, 7th ed., Copyright.COPYRGT. 1998 W. B. Saunders Company).

Mucositis

[032] Oral mucositis (OM) is a significant problem in patients receiving chemotherapy or radiation therapy. Estimates of oral mucositis in cancer therapy range from 40% of those receiving standard chemotherapy to 76% of bone marrow transplant patients. Virtually all patients who receive radiation therapy to the head and neck area develop oral complications. Up to 90% of hematopoietic stem cell transplant patients develop 0M; up to 77% of breast cancer patients develop OM; up to 68% of head and neck cancer patients receiving chemotherapy develop 0M; up to 63% of colorectal cancer patients develop 0M; up to 58% of esophageal cancer patients develop OM; up to 43% of malignant lymphoma patients develop 0M; and up to 38% of non-small cell lung cancer patients develop OM. Patients receiving targeted therapy will develop 0M with an incidence of up to 78% for Everolimus, up to 41% for Temsirolimus, up to 37% for Sunitinib, and up to 24% for Trastuzumab. Additional targeted therapeutics associated with the risk of developing 0M include bevacizumab, cetuximab, erlotinib, gefitinib and sorafenib.

[033] Mucositis is not only painful, but it also can limit adequate nutritional intake and decrease the willingness of patients to continue treatment. More severe mucositis with extensive ulceration may require costly hospitalizations with parenteral nutrition and narcotics. Mucositis diminishes the quality of life and may result in serious clinical complications. A healthy oral mucosa serves to clear microorganisms and provides a chemical barrier that limits penetration of many compounds into the epithelium. A mucosal surface that is damaged increases the risk of a secondary infection and may even prove to be a nidus for systemic infection. Mucositis may result in

the need to reduce dosage in subsequent chemotherapy cycles or to delay radiation therapy, which may ultimately affect patient response to therapy.

[034] Normally, cells of the mouth undergo rapid renewal over a 7- to 14-day cycle. Both chemotherapy and radiation therapy interfere with cellular mitosis and reduce the ability of the oral mucosa to regenerate. Cancer chemotherapeutic drugs that produce direct stomatotoxicity include the alkylating agents, antimetabolites, natural products, and other synthetic agents such as hydroxyurea and procarbazine hydrochloride. Typical sequelae of these cytotoxic agents include epithelial hyperplasia, collagen and glandular degeneration, and epithelial dysplasia. Mucositis is an inevitable side effect of radiation. The severity of the mucositis is dependent on the type of ionizing radiation, the volume of irradiated tissue, the dose per day, and the cumulative dose. As the mucositis becomes more severe, pseudomembranes and ulcerations develop. Poor nutritional status further interferes with mucosal regeneration by decreasing cellular migration and renewal.

[035] Direct stomatotoxicity is usually seen 5 to 7 days after the administration of chemotherapy or radiation therapy. In the nonmyelosuppressed patient, oral lesions heal within 2 to 3 weeks. The nonkeratinized mucosa is most affected. The most common sites include the labial, buccal, and soft palate mucosa, as well as the floor of the mouth and the ventral surface of the tongue. Clinically, mucositis presents with multiple complex symptoms. It begins with asymptomatic redness and erythema and progresses through solitary white elevated desquamative patches that are slightly painful to contact pressure. Following this large, acutely painful contiguous pseudomembranous lesions will develop with associated dysphagia and decreased oral intake. Histopathologically, edema of the retepegs is noted, along with vascular changes that demonstrate a thickening of the tunica intima with concomitant reduction in the size of the lumen and destruction of the elastic and muscle fibers of the vessel walls. The loss of the epithelial cells to the basement membrane exposes the underlying connective tissue stroma with its associated innervation, which, as the mucosal lesions enlarge, contributes to increasing pain. Oral infections, which may be due to bacteria, viruses, or fungal organisms, can further exacerbate the mucositis as well as lead to systemic infections. If the patient develops both severe mucositis and thrombocytopenia, oral bleeding may occur that is very difficult to treat.

[036] A mucositis grading system gives the physician the ability to assess the severity of the mucositis in terms of both the pain and the patient's ability to maintain adequate nutrition so that a treatment plan can be appropriately constructed. There are many different grading systems; most are based on two or more clinical parameters, including erythema, pain, and problems with eating. An example of a common grading system is that proposed by the National Cancer Institute, which uses a numbering scale of 0 to 4. Grade 0 means no mucositis; grade 1, the patient has painless ulcers, erythema, or mild soreness; grade 2, the patient has painful erythema, edema, or ulcers but can eat solid food; grade 3, the patient has painful erythema, edema, or ulcers and cannot eat solid food; and grade 4, the patient requires parenteral or enteral support.

[037] A standardized approach for the prevention and treatment of chemotherapy- and radiation-induced mucositis is essential; unfortunately, the efficacy and safety of most of the regimens have not been established. The prophylactic measures usually employed for the prevention of mucositis include chlorhexidine gluconate (Peridex), saline rinses, sodium bicarbonate rinses, acyclovir, amphotericin, and ice. Regimens commonly used for the treatment of mucositis and its associated pain include a local anesthetic such as lidocaine or Dyclone, Maalox or Mylanta, diphenhydramine (Benadryl), nystatin, or sucralfate. These agents are either used alone or in different combinations of the above medications made into a mouthwash. Other agents used less commonly include Kaopectate, allopurinol, vitamin E, beta-carotene, Kamillosan liquid, aspirin, antiprostaglandins, prostaglandins, MGI 209 (marketed as Oratect Gel), silver nitrate, and antibiotics. Oral and sometimes parenteral narcotics are used for pain relief. A new method utilizing capsaicin is currently under study to help relieve the pain. (Source: DeVita: Cancer: Principles and Practice of Oncology, 5th ed., Copyright.COPYRGT. 1997 Lippincott-Raven Publishers).

Oral Lichen Planus

[038] Lichen planus (LP) is a common, idiopathic skin disorder affecting approximately 2% of the adult US population. Although its behavior on the skin is predictable and manageable using topical corticosteroids, oral lichen planus (OLP) has a more variable clinical course and is less responsive to topical corticosteroid therapy.

There are multiple clinical presentations of OLP, and the disorders in some of these clinical forms can mimic many other types of oral lesions. Furthermore, some authors believe that certain clinical types of OLP may have a premalignant nature. Various drugs, topical and systemic, have been shown to induce lichenoid lesions through antigenic mechanisms.

[039] There is even good evidence emerging that amalgam and dental plaque can act as antigens to induce OLP in some patients. The plaque form of OLP is seen more often in smokers. Women appear to be affected more often than men. Not all persons who develop skin lesions develop OLP at the same time and vice versa. Those patients who develop skin lesions only are usually free of their LP in approximately 18 months; however, patients with OLP may have their lesions for up to 20 years. Thus, management strategies for the patient with OLP are markedly different than for its skin surface counterpart.

[040] The most common oral presentation of LP is the reticular form. These lesions appear as raised white, linear striations that often interlace in what is termed striae of Wickham. These striations are almost pathognomonic of the disorder. It should be noted that these linear lesions also accompany the erosive form of OLP and occur at the periphery of the eroded area. This is a significant diagnostic clue in the evaluation of the erosive type. The reticular form usually is observed on the buccal mucosa, often bilaterally. Several authors have noted that these lesions are adjacent to gold or silver amalgam restorations in many cases. The lesions are asymptomatic.

[041] The bullous form of OLP is uncommon, perhaps because the oral cavity is a very active region. The functions of chewing, swallowing, and speaking probably do not allow the bulla to remain intact for very long. The size of these lesions is variable, from a few millimeters to several centimeters. The plaque type of OLP appears as a nondescript leukoplakia that needs to be biopsied if no other diagnosis can be made for the lesion. These lesions appear as multiple diffuse, raised white plaques commonly on the buccal mucosa and tongue. Silverman et al have determined that patients with this form of LP tend to be smokers. This may place them at risk for transformation to dysplasia or carcinomatous change.

[042] The atrophic form of OLP can be seen concomitantly with the erosive or reticular forms. This is frequently the type of OLP seen on the gingiva of patients, com-

monly referred to as desquamative gingivitis. These lesions are symptomatic. The patient may complain of burning and pain while brushing. Because dental plaque has been implicated as a possible antigen, the patient will need to see a dentist for professional maintenance following initial corticosteroid treatment of the lesions.

[043] Erosive LP is the most painful form of OLP. As stated previously, these erosions are seen frequently with the reticular form adjacent to the area. Atrophic or plaque forms may be seen less commonly. Erosive LP may mimic oral cancer, erythema multiforme, lupus erythematosus, and candidiasis. Many drugs can produce lesions that look like erosive LP clinically. (Source: D. A. Miles and M. M. Howard, "Disorders affecting the oral cavity: Diagnosis and management of oral lichen planus", Dermatologic Clinics, 1996, 14(2), 281-290.)

Pemphigus

[044] Pemphigus is a rare, autoimmune blistering disease. Of the various forms of pemphigus, pemphigus vulgaris and paraneoplastic pemphigus affect the oral mucosa with regularity. The antigenic targets in pemphigus are components of the desmosome. Binding of autoantibodies to these antigenic proteins, desmogleins and desmoplakins, leads to dissolution of intercellular adhesion with resultant blister formation. Activity of the disease correlates with titers of pemphigus antibody, which can be detected in the serum of patients with the disease by indirect immunofluorescence testing.

[045] Pemphigus was often a fatal disease before the use of systemic corticosteroids. It has a chronic course, and control of the disease becomes more difficult with subsequent flares. The basis of treatment is immunosuppression to decrease antibody synthesis. Relapses may occur when immunosuppressive drugs are tapered. Paraneoplastic pemphigus remains a very difficult disease to treat and continues to have very high mortality rates.

[046] Historically, therapy for pemphigus was initiated with very high doses of prednisone. This initial high dosage proved to have so many adverse effects that in one early study 8% of patients died from complications of treatment (mainly infections) rather than from pemphigus. The authors recommend that pemphigus initially be

treated with prednisone, 60 to 80 mg daily, and generally no more than 100 mg daily. Studies have shown that this dosage is usually as effective as higher doses. If there is no response, but the patient remains stable, the authors recommend adding a second immunosuppressive agent rather than increasing the dose of steroids. Although there are no good controlled studies to support this practice, it is also being followed in the treatment of organ transplant rejection to decrease morbidity from corticosteroids. In patients in whom the disease must be rapidly controlled, higher doses of prednisone may be required to stabilize the patient.

[047] Successful treatment of pemphigus has been achieved with prednisone in combination with azathioprine, cyclosporine, cyclophosphamide, dapsone, and gold sodium thiomalate.

[048] Fleischli et al report the successful treatment of pemphigus vulgaris with pulse intravenous cyclophosphamide. Six of nine patients responded to therapy, and two patients achieved remission of skin lesions. One patient was able to discontinue prednisone completely. Two patients died of cardiac complications despite improvement of their skin disease. One patient developed sepsis that was successfully treated with intravenous antibiotics. The investigators concluded that pulse cyclophosphamide may be a useful adjunctive treatment for recalcitrant disease. Long-term side effects such as secondary malignancy may be less likely to result from this treatment than from perorally administered cyclophosphamide because of the lower cumulative doses. Intravenously administered cyclophosphamide should be reserved for patients with severe, recalcitrant disease because of the serious complications that may occur during therapy. (Source: J. L. Popovsky and C. Camisa, "New and emerging therapies for diseases of the oral cavity", Dermatologic Clinics, 2000, 18(1), 113-125.)

Radiation Proctitis

[049] Acute complications of pelvic radiation occur with distinct clinical courses and pathologic manifestations. The most frequent serious complication of pelvic radiation is small bowel damage, including thrombocytopenia, leukopenia, dysuria, and effects on the small bowel (diarrhea, abdominal cramping, and increased bowel frequency) and large bowel (acute proctitis, tenesmus, bloody and/or mucus discharge). Sig-

moidoscopy during treatment normally reveals an inflamed, edematous, and friable rectal mucosa consistent with acute radiation proctitis. These symptoms are usually transient and resolve within a few weeks following the completion of radiation therapy. They appear to be a function of the dose rate and fraction size rather than the total dose. The mechanism is primarily the depletion of actively dividing cells in what is otherwise a stable cell renewal system. In the small bowel, loss of the mucosal cells results in malabsorption of various substances including fat, carbohydrate, protein, and bile salts. The management of bowel-related complications usually involves the use of diphenoxylate and/or narcotics. The bowel mucosa usually recovers in 1 to 3 months following the completion of radiation. (Source: DeVita: Cancer: Principles and Practice of Oncology, 5th ed., Copyright.COPYRGT. 1997 Lippincott-Raven Publishers).

Stomatopharyngitis, in Sjogren's syndrome

[050] Sjögren syndrome is a disorder whose main features are dry eyes and a dry mouth. The condition typically develops gradually beginning in middle adulthood, but it can occur at any age.

[051] Sjögren syndrome is classified as an autoimmune disorder, one of a large group of conditions that occur when the immune system attacks the body's own tissues and organs. In Sjögren syndrome, the immune system primarily attacks the glands that produce tears (the lacrimal glands) and saliva (the salivary glands), impairing the glands' ability to secrete these fluids.

[052] Dry eyes may lead to itching, burning, a feeling of sand in the eyes, blurry vision, or intolerance of bright or fluorescent lighting. A dry mouth can feel chalky or full of cotton, and affected individuals may have difficulty speaking, tasting food, or swallowing. Because saliva helps protect the teeth and the tissues of the oral cavity, people with Sjögren syndrome are at increased risk of tooth decay and infections in the mouth.

[053] In most people with Sjögren syndrome, dry eyes and dry mouth are the primary features of the disorder, and general health and life expectancy are largely unaffected.

Ulcrative Colitis

[054] Inflammatory bowel diseases (IBD), including ulcerative colitis and Crohn's disease, are chronic inflammatory diseases of the gastrointestinal tract. They are diagnosed by a set of clinical, endoscopic, and histologic characteristics, but no single finding is absolutely diagnostic for one disease or the other. Moreover, some patients have a clinical picture that falls between the two diseases and are said to have indeterminate colitis.

[055] The inflammatory response in ulcerative colitis is largely confined to the mucosa and submucosa, but in Crohn's disease the inflammation extends through the intestinal wall from mucosa to serosa. Ulcerative colitis is confined to the colon, and colectomy is a curative procedure. Crohn's disease, in contrast, can involve any part of the gastrointestinal tract, although the distal small bowel and the colon are most commonly involved. Resection of the inflamed segment is not curative in Crohn's disease, and inflammation is likely to recur.

[056] In ulcerative colitis, inflammation begins in the rectum, extends proximally a certain distance, and then abruptly stops, with a clear demarcation between involved and uninvolved mucosa. In mild disease, there are superficial erosions, whereas in more severe disease, ulcers may be large but superficial, penetrating the muscularis mucosa only in very severe disease. Inflammatory polyps or pseudopolyps may be present. Most of the pathologic findings in ulcerative colitis are limited to the mucosa and submucosa; the muscularis propria is affected only in fulminant disease. Active ulcerative colitis is marked by neutrophils in the mucosa and submucosa and clumps of neutrophils in crypt lumens (crypt abscesses). There is mucus depletion, mucosal edema, and vascular congestion with focal hemorrhage. In addition to signs of acute activity, there are also signs of chronicity, with lymphoid aggregates, plasma cells, mast cells, and eosinophils in the lamina propria.

[057] The dominant symptom in ulcerative colitis is diarrhea, which is usually associated with blood in the stool. Bowel movements are frequent but small in volume as a result of irritability of the inflamed rectum. Urgency and fecal incontinence may limit the patient's ability to function in society. Other symptoms include fever and pain, which may be in either lower quadrant or in the rectum. Systemic features--fever,

malaise, and weight loss--are more common if all or most of the colon is involved and may have a greater effect than diarrhea on the patient's ability to function. Some patients, especially elderly persons, complain of constipation rather than diarrhea because rectal spasm prevents the passage of stool. The initial attack of ulcerative colitis may be fulminant with bloody diarrhea, but more commonly the disease begins indolently, with non-bloody diarrhea progressing to bloody diarrhea. Ulcerative colitis can present initially with any extent of anatomic involvement, from disease confined to the rectum to pancolitis. Most commonly, ulcerative colitis follows a chronic intermittent course with long periods of quiescence interspersed with acute attacks lasting weeks to months; however, a significant percentage of patients suffer a chronic continuous course. (Source: Goldman: Cecil Textbook of Medicine, 21st Ed).

[058] Additional mucosal disorders useful for treatment using the mucoadhesive compositions of the present invention include vaginal mucositis, mucositis in the stomach, in the intestines, and in other tissues or organs of the alimentary canal where mucositis is occurring. In these cases, it may be advantageous to adjust the composition to obtain relative viscosity of the composition so that it more readily reaches the tissues by oral, rectal or vaginal administration.

[059] In the diseases and disorders listed above, there are either no adequate treatment options, or the treatments, while demonstrating success, may lead to the development of significant adverse side-effects.

[060] It is an aim of the present invention to provide viscous, mucoadhesive liquid formulations to be used for the prevention and treatment of mucocutaneous disorders. The composition may be used with or without one or more active pharmaceutical agents. These formulations are especially beneficial in diseases and conditions in which a wide area of the mucosal surface requires treatment, but the formulations may also be used in treating small areas of the mucosal surface.

[061] In order that mucocutaneous disorders are treated effectively, it is preferred that the lesion is in contact with the liquid mucoadhesive composition for the period of time required to derive benefit. To grant such benefit, this invention describes mucoadhesive, viscous liquid formulations which may or may not contain one or more pharmaceutically active ingredients. The liquid can readily be applied to the affected region of the mucosa by methods known in the art, while the high viscosity and mu-

coadhesion will cause liquid to remain in contact with the lesion for extended periods. The formulations of the present invention may be applied to treat mucocutaneous lesions in a variety of body compartments, including, but not limited to, the oral cavity, the nasal cavity, the esophagus, the gastro-intestinal tract, the rectum, the bladder, and the vagina.

[062] Furthermore, the viscous, mucoadhesive liquid formulations of the current invention may be used to deliver one or more pharmaceutically active compounds to the mucosal surface, either for the prevention or treatment of diseases and disorders of the mucosa, or for delivery of the pharmaceutically active compound(s) to the systemic circulation by transfer through the mucosa.

SUMMARY OF THE INVENTION

[063] Generally, in one aspect the present invention discloses an aqueous mucoadhesive and bioadhesive composition for the treatment or prevention of diseases or disorder related to mucous membrane.

[064] In another aspect, the aqueous composition may comprise the combination of mucoadhesive agent, bioadhesive agent, a pharmaceutically active agent, natural polymer and cannabinoid.

[065] In yet another aspect, the present invention discloses composition that may be stable from solid to liquid state, and the use of these compositions to coat mucocutaneous surfaces, such as those in the oral cavity, the nasal cavity, the gastrointestinal and respiratory tracts, the eye, the vagina, and the bladder, etc. to prevent and/or treat mucosal diseases and disorders, including those which are ulcerative, inflammatory, and/or erosive.

[066] In still another aspect, the present invention discloses the composition wherein the dosage forms are compositions sufficiently used to coat a wide area of the mucosal surface, but are also bioadhesive and mucoadhesive useful to provide prolonged retention on the surface of the mucosa.

[067] In yet another aspect, the present invention discloses the compositions from liquid to solid may be used without a known pharmaceutically active compound. One or more pharmaceutically active compounds may be included in the composition to provide additional benefit in the topical treatment of diseases, disorders and conditions of the mucosa, or for drug delivery through the mucosa to the systemic circulation.

[068] Specifically, in accordance with the present invention there is provided an aqueous mucoadhesive and bioadhesive composition comprising all natural ingredients for the sustained and effective treatment or prevention of mucosal diseases and disorders.

[069] Other aspects of the present invention are disclose in the appended drawings and the following description.

DETAILED DESCRIPTION OF THE INVENTION

[070] The present invention may be understood more readily by reference to the following detailed description of the invention taken in connection with the accompanying drawing figures, which forms a part of this disclosure. It is to be understood that this invention is not limited to the specific devices, methods, conditions or parameters described and/or shown herein and that the terminology used herein is for the example only and is not intended to be limiting of the claimed invention. Also, as used in the specification including the appended claims, the singular forms 'a,' 'an', and 'the' include the plural, and references to a particular numerical value includes at least that particular value unless the content clearly directs otherwise. Ranges may be expressed herein as from 'about' or 'approximately' another particular value. When such a range is expressed another embodiment. Also, it will be understood that unless otherwise indicated, dimensions and material characteristics stated herein are by way of example rather than limitation, and are for better understanding of sample embodiment of suitable utility, and variations outside of the stated values may also be within the scope of the invention depending upon the particular application.

[071] Embodiments will now be described in detail with reference to the accompanying drawings. To avoid unnecessarily obscuring the present disclosure, well-known features may not be described or substantially the same elements may not be redundantly described, for example. This is for ease of understanding.

[072] The drawings and the following description are provided to enable those skilled in the art to fully understand the present disclosure and are in no way intended to limit the scope of the present disclosure as set forth in the appended claims.

[073] The present invention discloses a composition for the treatment or prevention of mucocutaneous diseases and/or disorders. In one embodiment, the aforementioned composition of the present invention, comprises an amount of a bioadhesive and mucoadhesive effective to coat the mucocutaneous area being treated and may also contain a therapeutically or prophylactically active drug for a mucocutaneous disorder.

[074] In another embodiment of the present invention, the aforementioned composition described herein is useable in the treatment or prevention of a mucocutaneous disorder. This composition comprises an amount of a bioadhesive and mucoadhesive to form an effective coat in the mucocutaneous area being treated and can include a combination of therapeutic or prophylactic drugs for mucocutaneous disorders.

[075] In another embodiment, the mucoadhesive agent disclosed in the present invention is a naturally occurring compound. The mucoadhesive agent is generally present at a concentration between 0.01 w/w% and about 10.0 w/w% in the aforementioned composition. In another embodiment, the mucoadhesive agent of the present invention is sodium alginate and the preferred bioadhesive is hyaluronic acid. The composition of the present invention is preferably at a pH between about 5.5 and about 8.5. Particularly, sodium alginate is highly effective and suitable in disclosed composition herein.

[076] Sodium alginate is unique and preferred for a variety of reasons and provides a variety of unexpected benefits to the composition. For example sodium alginate provides antimicrobial activity to the mucoadhesive composition. In addition, sodium

alginate provides anti-inflammatory activity. See Maroon et al., Surg. Neurol. Int., 2010, 1:80, PMCID: PMC3011108. Furthermorae, sodium alginate is a natural product, and compositions containing greater than 70% wt/wt natural ingredients can be labeled as a "natural" product in the commercial marketing of the mucoadhesive composition. A preferred composition typically contains from 0.01 to 10.0 wt/wt % of sodium alginate, preferably 0.01 to 5.0 wt/wt %, and more preferably about 1.0 to 2.0 wt/wt %. A particularly preferred composition contains 1.80 wt/wt % sodium alginate. Sodium alginate has been extensively characterized in the scientific literature, and its preparation and purification has also been described extensively. See, for example, Krol et al, Int.J.Mol.Sci. 2017, 18: 678; Smidsrod, Carbohydrate Research 1973, 27:107; and Huag et al, Acta Chemica Scandinavica 1969, 23: 2955.

[077] It is known that polyanionic carbohydrate polymers and oligomers can have a beneficial effect in the treatment of mucosal disorders. For example, pentosan polysulfate and hyaluronic acid are known to provide benefit to patients with interstital cystitis (Morales A, et al, Treatment of refractory interstitial cystitis, Int Urogynecol J Pelvic Floor Dysfunct 1996; 7(4):215-20). It is quite possible that other polyanionic and polycationic compounds, whether carbohydrate or of natural origin, may also provide benefit in the prevention and treatment of mucosal disorders. Linear and partially cross-linked polyanionic polymers may be included in the compositionue/'P O;sed in the mucoadhesive composition. Additional polymers which are useful in the mucoadhesive composition include carboxy methyl cellulose, hydroxy propyl methyl cellulose, Carbopol 934, Carbopol 971, Noveom AA, tragacanth, sodium alginate, polycarbophil, hydroxyl ethyl cellulose, and the like polymers.

[078] In another embodiment of the present invention, the aforementioned composition may contain at least 70 % wt/wt natural ingredients such that the composition can be labeled as a "natural" product for marketing purposes under current rules in the US for natural products. This natural designation provides particular advantages, and provides an additional reason for sodium alginate being particularly preferred mucoadhesive ingredient in the mucoadhesive compositions of the present invention. This is in contrast to the use of, for example Carbopol 934, Carbopol 971, Noveom AA, or polyvinylpyrrolidine (PVP), as examples instead, which is a synthetic polymer, as a mucoadhesive. These advantages include but are not limited to the nutritional advantage where there would not be any undesirable effects caused by a

synthetic polymer, including undesirable aspects as yet to be identified through the use of such synthetic materials. An additional advantage to natural ingredient designation is the intrinsic appeal to the health-conscious consumer and to facilitate targeted marketing to the natural products consumer. Further benefits to a natural product include the placebo effect associated with the patient who uses the mucoadhesive composition, whereby the patient understands the product is natural and is thereby free from any stress associated negative perceptions about using a mucoadhesive composition containing synthetic polymers or materials. Further advantages include the ability to swallow and thereby consume the mucoadhesive composition without any adverse side effects associated with a synthetic composition. This is particularly important when a physician or care provider is assessing the risk versus benefit analysis for any particular therapeutic or care plan.

[079] It is pertinent to note that the utilization of hyaluronic acid is particularly preferred in the aforementioned composition. Hyaluronic Acid is unique and preferred for a variety of reasons and provides a variety of unexpected benefits to the composition. Hyaluronic acid is a substance that is naturally present in the human body. It is found in the highest concentrations in fluids in the eyes and joints. Hyaluronic acid (HA), is a polyanionic polysaccharide that consists of N-acetyl-D-glucosamine and β-glucoronic acid. Hyaluronic acid is the surface-anchored bioadhesive ligand in the composition for its unique viscoelastic nature and a drug delivery agent for ophthalmic, nasal, oral, dermal, pulmonary, intestinal, vaginal, and rectal routes. For example hyaluronic acid provides wound healing in dermal and mucosal tissues. See Chen M et al; Technical center, Guangzhou Weimeizi Industrial Co., Ltd., Guangzhou 510665, PR China; Collaborative Research Center of Guangzhou Weimeizi Industrial Co., Ltd and Rutgers University, 2019, PMID: 30465936, DOI: 10.1016/j.archoralbio.2018.10.027

[080] In another embodiment of the present invention, a mucoadhesive liquid, solid, semi-solid, gel, gummy or powder composition may contain one or more pharmaceutically active ingredients including anesthetic, analgesic, antihistamine, antiseptics, antioxidants, anti-fungals, antibacterials, anti-infectives, antiemetics, antidiarrheals, antifungals, anti-inflammatories, antimicrobial agents, astringents, amino acids, cleansing agents, cooling agents, corticosteroids, emollients, flavorants, flavonoids, healing agents, humectants, liposomes, moisturizers, peptides, prebiotics, probiotics,

solubilizing agents, styptic agents, sweeteners, vasodilators and other excipients known in the art of composition of pharmaceutical products. Further, the aforementioned composition may preferably include a therapeutically or prophylactically effective amount of cannabidiol.

In another embodiment of the present invention, a bioadhesive liquid, solid, semi-solid, gel, gummy or powder composition can include plant lectins, nano-hydroxapatite, β-defensin-3 peptide, salamander secretions, snail mucus, fenugreek gum, polysaccharides, fruit sugars, and dextran.

[081] In another embodiment of the present invention, other components of the compositionmay can include sorbic acid, citric acid, glycerin, synsepalum dulcficum, and erythritol or xylitol, alone or in combination with each other and/or the other excipients of the compositionmay have a beneficial effect. Other preservatives, humectants, emulsifying agents, amino acids, analgesics, anesthetics, antihistamines, antiseptics, antioxidants, anti-fungals, antibacterials, antiemetics, antidiarrheals, anti-inflammatory, antimicrobial agents, astringents, bowel obstruction agents, cellular regeneration, cleansing agents, cooling agents, corticosteroids, emollients, flavorants, flavonoids, healing agents, humectants, moisturizers, peptides, solubilizing agents, styptic, vasodilators, and other excipients known in the art in the composition of pharmaceutical products, alone or in combination, may also provide for, or enhance, the beneficial properties on mucosal surfaces, when formulated to provide a viscous, mucoadhesive solution.

[082] In another embodiment of the present invention, the aforementioned composition for the prevention and treatment of mucosal diseases and disorders may additionally be formulated with one or more compounds known to be pharmaceutically active. Addition of further pharmaceutically active compounds could provide greater benefit to patients in the prevention and treatment of mucosal disorders. Examples of pharmaceutically active compounds which could be incorporated in the mucoadhesive solutions of this invention as provided later in this section.

[083] In another embodiment of the present invention, the aforementioned composition may contain a combination of mucoadhesives or other ingredients, in so far as those other ingredients provide desirable properties. For example the composition may further include chitosan, carrageenan, or hyaluronic, in amounts to contribute to

the relative viscosity of the composition, or to provide additional useful properties to the composition. For example, hyaluronic acid is known to promote moisture retention and otherwise to provide healing effects and may further contribute to viscosity. Preferred polymer ingredients which contribute to the viscosity and mucoadhesive properties are natural polymers, such as agar, agarose, albumin, alginate, arame, bladderwrack, carrageenan, chitin, chitosan, collagen, dextran, dulse, gum Arabic, gelatin, guar gum, hyaluronic acid, hydroxyl propyl methyl cellulose, irish moss, lectin, manikara zapota, mastic gum, moringa gum, mytilus edulis, neem gum, nori, pectin, psyllium, sea palm, snail slime or mucus, sodium caroxymethylcellulose, soluble starch, sunflower lecithin, tamarind seed polysaccharide, tragacanth, xanthum gum, brown seaweed, sodium alginate.

[084] In another embodiment of the present invention, the aforementioned composition may comprise the combination of sodium alginate and hyaluronic acid. This combination of sodium alginate and hyaluronic acid is preferred because there is a synergistic cellular interaction with this combination that provides an antibacterial activity. This composition preferably includes a ratio of sodium alginate and hyaluronic acid in amounts which provide demonstrable enhancement and controlled release of lidocaine activity. This combination is also particularly preferred because sodium alginate and hyaluronic acid are natural components, which can contribute to the designation of a “natural” product for marketing purposes. Anirudhan et al, Department of Chemistry, School of Physical and Mathematical Sciences, University of Kerala, India, Carbohydrate Polymers, 2016 , 152 (2016) 687-698.

[085] In another embodiment of the present invention, a further preferable composition of a mucoadhesive composition of the present invention comprises sodium alginate and chitosan is disclosed herein. This combination of sodium alginate and chitosan is preferred because there is a synergistic cellular interaction with this combination that provides an antibacterial activity. Yong-Haoo et al, Institute of Forestry and Pomology, J. Appl. Polym.Sci. 2015, Volume102, Issue 9 September 2014 Pages 3056-3065132, 41898. This composition preferably includes a ratio of sodium alginate and chitosan in amounts which provide demonstrable antibacterial activity. This combination is also particularly preferred because sodium alginate and chitosan are natural components, which can contribute to the designation of a “natural” product for marketing purposes.

[086] Similarly, a preferred composition of a mucoadhesive composition of the present invention comprises sodium alginate and hyaluronic acid (HA). This combination of sodium alginate and HA is preferred because HA contributes moisture retention and the capacity to further promote healing to the mucoadhesive composition. This composition preferably includes a ratio of sodium alginate and HA in amounts which provide demonstrable moisture retention or healing activity. This combination is also particularly preferred because sodium alginate and HA are natural components, which can contribute to the designation of a "natural" product for marketing purposes. Neuman et al, J. Pharm Pharm Sci, Hyaluronic Acid and Wound Healing, 2015 18(1) 53-60, 2015

[087] In another embodiment of the present invention, the aforementioned composition may comprise additional combinations which contain natural ingredients can include agar, agarose, albumin, alginate, arame, bladderwrack, carrageenan, chitin, chitosan, collagen, dextran, dulse, gum Arabic, gelatin, guar gum, hyaluronic acid, hydroxyl propyl methyl cellulose, irish moss, lectin, manikara zapota, mastic gum, moringa gum, mytilus edulis, neem gum, nori, pectin, psyllium, sea palm, sodium caroxymethylcellulose, soluble starch, sunflower lecithin, tamarind seed polysaccharide, tragacanth, xanthum gum, brown rice, or a variety of celluolose derivatives. Formulations with one or more of these additional natural ingredients are preferred because as natural components they can contribute to the designation of a "natural" product for marketing purposes.

[088] In another embodiment of the present invention, the aforementioned composition may further comprise pharmaceutically active compounds which may be formulated with the mucoadhesive agent in liquid, semi-solid, gel, gummy, solid in the form of lozenges or powder formulations of the current invention, either for topical treatment of a mucosa, or for transfer of the pharmaceutically active ingredient to the systemic circulation can include, either alone or in combination, one or more of the following classes of drugs: anti-allergy compounds, anti-inflammatory analgesic agents, steroidal and non-steroidal anti-inflammatory agents, anabolic steroids, analgesics, antiemetics, antihistamines, local anesthetics, amino acids, bactericides, cooling agents, cortecosteroids, disinfectants, healing agents, peptides, vasoconstrictors, compounds that promote wound-healing, hemostatics, chemotherapeutic agents, antibiotics, keratolytics, cauterizing agents, and antiviral drugs. Other clas-

ses of pharmaceutically active agents may also be formulated with the mucoadhesive liquid, solid, semi-solid, gel, gummy or powder formulations of the current invention.

[089] In another embodiment of the present invention, the aforementioned composition may further contain one or more cannabinoids as an active ingredient, in an amount to provide a therapeutically or prophylactically effective outcome upon administration of the mucoadhesive composition as described herein, typically in an amount of about 0.01-15% wt/wt. Exemplary cannabinoids are cannabidiol (CBD), tetrahydrocannabinol (THC), cannabidiolic acid (CBD-A), cannabigerolic acid (CBN-A), cannabigerol (CBG), cannabinolic acid (CBN-A), cannabichromenic acid (CBC-A), cannabichromene (CBC), and cannabinol (CBN), the structures and preparation of which are described in US Patent 7,807,711. Cannabidiol (CBD) is particularly preferred in view of its antioxidant, anti-inflammatory, anesthetic, antiemetic and analgesic properties that make it useful in the claimed formulations. See e.g., Pan et al., J. Pharmacol. Exp. Ther., 2009, 328:708-714; Cassol et al., Brain Res., 2010, 1348:128-138; Burstein, Bioorg. Med. Chem., 2015, 23:1377-1385; Friedman et al, N. Engl.J. Med., 2015, 373:1048-1058; Rahn et al., Neurotherapeutics, 2009, 6:713-737; Costa et al, Eur J. Pharmacol. 2007, 556:75-83; Calignano et al., Nature, 1998, 394:277-281. CBD can be 200extracted from cannabis by a variety of published methods, in particular as described by Giacoppo et al, DARU J Pharma. Sci., 2015, 23:48. Furthermore, cannabinoids and CBD can be obtained from a variety of vendors in a range of concentrations. A preferred vendor for CBD is HempMeds PX, LLC, hempmedspx.com, which provides certified pure CBD available as a dried material at 99.8 wt%. A preferred mucoadhesive liquid composition contains 0.01-15.0% (wt/wt), preferably about 0.01-10.0%, and more preferably 0.4% CBD.

[090] In another embodiment of the present invention, the mucocutaneous disorders treatable by the methods and compositions of the present invention may include but not limited to oral, vaginal or rectal mucositis, Bechet's disease, apthous ulcer, bullous pemphigoid, chemical cystitis, radiation cystitis, erythema multiforme, esophagitis, interstitial cystitis, oral Lichen planus, pemphigus, sjogren's syndrome, stomatitis, xerostomia, radiation proctitis, stomatopharyngitis, vaginitis, bacterial vaginosis, keratitis sicca, conjunctivitis, dry eye disease, rhinitis, or ulcerative colitis. There are also painful ulcerative disorders of mucosal surfaces which result as an adverse

side-effect in certain therapies, including certain medications treating various diseases such as rheumatoid arthritis, HIV, such as dental procedures and appliances, chemotherapy, radiation therapy or stem cell transplantation. Examples of such side-effects include mucositis, esophagitis, and radiation proctitis. Many other ulcerative or inflammatory mucocutaneous diseases are known, including xerostomia, stomatitis (including caused by certain medications or medical and non-medical apparatus'), and the like.

[091] In another embodiment, the present invention involves a method for the prevention or treatment of mucocutaneous disorders. This method involves identifying a patient having or possibly developing a mucocutaneous disorder. Next in this method is the administration to the patient of a composition comprising a bioadhesive and mucoadhesive agent in an amount effective to prevent or treat the mucocutaneous disorder. Of course, this composition may and often does include a viscosity-inducing agent and/or a viscosity-enhancing concentration of bioadhesive and mucoadhesive. Mucocutaneous disorders treatable by this method are described above. This composition is often more useful when possessing pseudoplastic behavior, which provides for reduced viscosity during application, allowing the composition to cover the mucosa more readily, and for increased viscosity of the composition when in place on a mucocutaneous area. In terms of the length of treatment, this will vary according to the severity and type of disorder. It is expected that the alleviation of mucocutaneous disorders should be visible to anyone treating the patient and that the method of treatment should continue until recovery is clear. This may take from hours to days to weeks, depending upon the situation. Preferred mucoadhesive agents for this method are described herein. Likewise, for viscosity-inducing agents.

[092] In another embodiment of the present invention, the aforementioned composition described herein are useful for the prevention and treatment of disorders of mucous membranes in humans and animals. The liquid, semi-liquid, gel, semi-solid, or solid form of other formulations of the present invention are ideally suited to treat diseases and disorders which affect a wide area of the mucosal surface, but they also provide the opportunity to treat discrete, localized lesions, especially in the oral cavity. The mucous membranes which may be treated by the compositions described in this patent include, but are not limited to, those in the oral cavity, the nasal cavity, the gastrointestinal and respiratory tracts, the eye, the vagina, and the blad-

der. Inflammatory, erosive, and/or ulcerative diseases which can be treated by topical application of the compositions described in this patent include, but are not limited to, aphthous ulcers, Behcet syndrome, bullous pemphigoid, chemical or radiation-induced cystitis, erythema multiforme, esophagitis, interstitial cystitis, oral or rectal mucositis, oral lichen planus, pemphigus, rhinitis, conjunctivitis, uveitis dry eye syndrome, vaginitis, bacterial vaginosis, stomatitis, xerostomia, and radiation proctitis. In conditions such as aphthous ulcers, chemical or radiation-induced cystitis, mucositis, and radiation proctitis, when the onset of the inflammatory, erosive, and/or ulcerative condition may be forecast (for example, by prodromal sensations in the case of aphthous ulcers, and by initiation of chemotherapy and/or radiation therapy in the treatment of cancer), the compositions of this invention might be applied prior to the formation of lesions, or at the commencement of therapy to prevent or delay the onset of inflammatory, erosive, and/or ulcerative lesions.

[093] In another embodiment of the present invention, the mucoadhesive/bioadhesive agents are designed to adhere to mucosal tissues thereby creating a barrier to protect the tissue. However, if the tissue is damaged or inflamed, then pain exists in the region, delivering a pain reliever through a mucoadhesive/bioadhesive enables the tissue to absorb and prolong the release of the pain aid on contact and the patient experiences pain relief. This novel mucoadhesive combined with a natural bioadhesive provide drug retention behavior in the composition. See Anirudhan TS et al, Department of Chemistry, School of Physical and Mathematical Sciences, University of Kerala, Kariavattom, Trivandrum-695 581, Kerala, India, 2016, PMID: 27516320 DOI: 10.1016/j.carbpol.2016.06.101.

[094] Aqueous solutions of pharmaceutically-active compounds are well known in the art as convenient drug delivery formulations. Such formulations are most useful for oral delivery, when the solution is swallowed, and the drug is presented to the stomach and gastrointestinal tract in a form which is amenable to rapid absorption. Aqueous solutions are also used to deliver drugs to mucosal tissue. In general, aqueous solutions used to deliver pharmaceuticals tend to be non-viscous and non-mucoadhesive. For oral delivery, this property is undesirable, as it minimizes the amount of drug which is retained in the oral cavity and esophagus, while maximizing what was delivered to the stomach and gastrointestinal tract.

[095] For topical treatment of mucosal membranes, aqueous solutions of pharmaceutically-active compounds offer the advantage over other dosage forms in that a wide area of the mucosa can be readily covered with the solution, which is of benefit if the area to be treated is not a single, discrete region. Also, mucosa not readily accessible can be treated using aqueous solutions of pharmaceutically-active compounds and simple methods of application. However, formulations which are non-mucoadhesive are less than ideal for delivery of drugs to mucosal surfaces. Such solutions will be rapidly removed from the area being treated, for example, because the liquid flows from the site of application under the influence of gravity, and/or because the natural secretions of mucosal membranes carry the solution from the site of application.

[096] Mucoadhesive formulations are well known in the art. However, known formulations intended for extended drug delivery to (or close to) the site of application of a mucoadhesive composition are either solids or semi-solids. Examples of the former include tablets, powders, lozenges, gummies, and films. Examples of mucoadhesive semi-solids include gels, gummies, pastes, ointments, and creams. Few, if any, examples are known in which a mucoadhesive is used as a drug delivery system.

[097] In another embodiment of the present invention, the stable, viscous, mucoadhesive liquid composition disclosed in the present invention may be applied to mucosal membranes for the delivery of pharmaceutically active compounds to the mucosal membranes for prevention and/or treatment of disorders or diseases of these membranes, or for the delivery of pharmaceutically active compounds to systemic circulation by passage through the mucosal membrane. The liquid may be applied, e.g., to the following mucosal surfaces; the oral cavity, the nasal cavity, the gastrointestinal and respiratory tracts, ocular, rectal tissues, the vagina, and/or the bladder. The formulations of the current invention may also be applied to other mucous membranes for the prevention and treatment of disorders and diseases. Many methods known in the art for the delivery of liquids to body compartments may be used.

[098] In another embodiment of the present invention, for the treatment of disorders and diseases of the oral cavity, the preferred stable mucoadhesive liquid, semi-solid, gummy and solid lozenge or powder composition of the present invention may be taken by mouth and distributed throughout the oral cavity by a swishing action, suck-

ing, or by the patient adopting a slow circulating movement of the head. Excess solution can either be swallowed or expelled.

[090] In another embodiment of the present invention, for the treatment of disorders and diseases of the esophagus, the stable, mucoadhesive liquid composition of the present invention can be swallowed with minimal contact of the oral cavity, or administered by gavage, or by spraying the liquid into the throat.

[100] In another embodiment of the present invention, for the treatment of disorders and diseases of the nasal cavity, the stable, mucoadhesive liquid composition of the present invention can be delivered as droplets or by spraying the liquid into the nose.

[101] In another embodiment of the present invention, for the treatment of disorders and diseases of the bladder, the stable, mucoadhesive liquid composition of the current invention can be delivered by intravesical or encapsulated administration.

[102] In another embodiment of the present invention, for the treatment of disorders and diseases of the eye, the stable mucoadhesive liquid composition of the current invention can be delivered as droplets into the eye.

[103] In another embodiment of the present invention, for treatment of disorders and diseases of the rectum and lower gastrointestinal tract, the stable, mucoadhesive liquid, solid, or semi-solid composition of the present invention can be administered by catheter, enema or suppository. In addition, for the treatment of the anus, a mucoadhesive liquid composition can be administered by topical treatment.

[104] Other methods to apply the stable, mucoadhesive liquid, semi-solid, gel, gummy, solid and powder composition of the present invention to mucosal tissues are known to those skilled in the art.

[105] In another embodiment of the present invention, pharmaceutically active compounds which may be formulated with the bioadhesive in liquid, semi-solid, gel, gummy, solid in the form of lozenges or powder composition disclosed herein, either for topical treatment of a mucosa, or for transfer of the pharmaceutically active ingredient to the systemic circulation can include, either alone or in combination, one or more of the following classes of drugs: anti-allergy compounds, anti-inflammatory analgesic agents, steroidal and non-steroidal anti-inflammatory agents, anabolic steroids, analgesics, antiemetics, antihistamines, local anesthetics, amino acids,

bactericides, cooling agents, cortecosteroids, disinfectants, healing agents, liposomes, peptides, prebiotics, probiotics, vasoconstrictors, compounds that promote wound-healing, hemostatics, chemotherapeutic agents, antibiotics, keratolytics, cauterizing agents, and antiviral drugs. Other classes of pharmaceutically active agents may also be formulated with the bioadhesive liquid, semi-solid, solid, gummy and powder formulations of the current invention.

[106] In another embodiment of the present invention, particular preferred formulations include analgesics or other pain reliever components, including the local anesthetics mentioned herein below, but in particular further including natural pain relievers. Exemplary natural anti-inflammatory agents useful for pain relief are well known in the art. See for example, Maroon et al., Natural anti-inflammatory agents for pain relief, Surgical Neurology International. 2010; 1:80. doi:10.4103/2152-7806.73804. Preferred natural analgesics include peppermint essential oil, willow bark powder, boswellia, menthol, curcumin, tulsi, cayenne, or turmeric extract or turmeric powder in amounts sufficient to provide analgesic benefits. These natural analgesics are particularly preferred because as a natural component they can contribute to the designation of a natural product for marketing purposes, and for the other benefits mentioned herein regarding advantages associated with use of natural ingredients in a mucoadhesive composition of the present invention.

[107] In another embodiment of the present invention, examples of anti-inflammatory analgesic agents include acetaminophen, methyl salicylate, monoglycol salicylate, aspirin, mefenamic acid, flufenamic acid, indomethacin, diclofenac, alclofenac, diclofenac sodium, ibuprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, sulindac, fenclofenac, clidanac, flurbiprofen, fentiazac, bufexarnac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, tiaramide hydrochloride, etc. In preferred formulations, the anti-inflammatory agent can be one or more of the natural products Aloe Vera, Boswellia Oil/Extract, Cannabinoids (Cannabidiol Oil), Beta Glucan (1,3), Ginger, Glutamine, Honey, L-carnitine, Lemon Extract, Olive Leaf Extract, Tulsi (Holy Basil Oil), Witch Hazel, Green Tea, Licorice (root extract), Calendula, Bee Propolis, Glucosamine, Goji Berry Extract, Myricetin, Chamomile, Hesperidin, Lemon Balm, Coffee, Turmeric, etc.

[108] In another embodiment of the present invention, examples of anabolic steroids include testosterone and oxandrolone.

[109] In another embodiment of the present invention, examples of antihistamines include diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride, chlorpheniramine maleate, isothipendyl hydrochloride, tripelennamine hydrochloride, promethazine hydrochloride, methdilazine hydrochloride, cetirizine, brompheniramine, clemastine, fexofenadine, loratadine, etc.

[110] In another embodiment of the present invention, examples of analgesics include menthol, boswellia oil extract, aspirin, ibuprofen, naproxen, dextromethorphan, NSAIDS, bovine colostrum, cyclosporine A, hops, mustard oil, black cumin, turmeric, willow bark extract, wintergreen oil, myricetin, and the like.

[111] In another embodiment of the present invention, examples of local anesthetics include dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, p-buthylaminobenzoic acid 2-(die-ethylamino)ethyl ester hydrochloride, procaine hydrochloride, cetacean, oraqix, tetracaine, tetracaine hydrochloride, carbamazepine, dibucaine, dibucaine hydrochloride, chloroprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, piperocaine hydrochloride, dyclonine, dyclonine hydrochloride, bupivacaine, butamben, cannabanoids, carbamazepine, ketamine, nupercainal, oxybuprocaine, prilocaine, pramoxine, proparacaine, proxymetacaine, tetracaine, peppermint, cayenne, peperine, capsaicin, cloves, ashwagandha extract, alphalipoic acid, african mango, phenylalanine, thuja, valerian, nigell sativa, mustard oil, cyclosporine A, tulsi, wintergreen, turmeric, curcumin, etc.

[112] In another embodiment of the present invention, examples of bactericides and disinfectants include thimerosal, phenol, thymol, benzalkonium chloride, benzethonium chloride, chlorhexidine, povidone iodide, cetylpyridinium chloride, eugenol, miconazole nitrate, hydrogen peroxide, trimethylammonium bromide, aloe vera, beta glucan 1, 3, honey, lemon extract, olive leaf extract, peppermint oil, sorbic acid, boswellia oil/extract, calendula, lactobacillus acidophilus, lemon extract, maitake, Manuka honey, lemongrass extract/oil, neem extract/oil, olive leaf, tea tree oil, turmeric, moringa seed extract, snail mucus, etc.

[113] In another embodiment of the present invention, examples of vasodilators include naphazoline nitrate, tetrahydrazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tramazoline hydrochloride, L- Citrulline L-Arginine etc.

[114] In another embodiment of the present invention, examples of hemostatics include thrombin, phytonadione, protamine sulfate, aminocaproic acid, tranexamic acid, carbazochrome, carbaxochrome sodium sulfanate, rutin, hesperidin, etc.

[115] In another embodiment of the present invention, examples of chemotherapeutic drugs include sulfamine, sulfathiazole, sulfadiazine, homosulfamine, sulfisoxazole, sulfisomidine, sulfamethizole, nitrofurazone, taxanes, platinum compounds, topoisomerase I inhibitors, and anthracycline, etc.

[116] In another embodiment of the present invention, examples of antibiotics include penicillin, meticillin, oxacillin, cefalotin, cefalordin, erythromeycin, lincomycin, tetracycline, chlortetracycline, oxytetracycline, metacycline, chloramphenicol, kanamycin, streptomycin, gentamicin, bacitracin, cycloserine, and clindamycin.

[117] In another embodiment of the present invention, examples of antibacterials include aloe vera, beta glucan 1,3, honey lemon extract, olive leaf extract, peppermint, sorbic acid, benzalkonium chloride solution, benzoic acid, hydrogen peroxide, miconazole nitrate, etc.

[118] In another embodiment of the present invention, examples of antifungals include aclovir, fluconazole, diflucan, chlorhexidine, clotrimazole, fungi zone, miconazole nitrate, nystatin, candicidin, fungizone, nystatin, voriconazole, posaconazole, itraconazole, tea tree oil, black walnut, cinnamon, elecampane, garlic, oregano oil, l-histidine, melaleuca oil, mycology, olive leaf oil, rose oil, palmerosa oil, propolis, tulsi oil, menthol, pau d' arco, peppermint, lemon, petitgrain oil, citronella oil, etc.

[119] In another embodiment of the present invention, examples of keratolytics include salicylic acid, podophyllum resin, podolifox, and cantharidin. Examples of cauterizing agents include the chloroacetic acids and silver nitrate.

[120] In another embodiment of the present invention, examples of antiviral drugs include protease inhibitors, thymadine kinase inhibitors, sugar or glycoprotein syn-

thesis inhibitors, structural protein synthesis inhibitors, attachment and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, ganciclovir, sage, elderberry, ginger, licorice, oregano, green tea, apple cider vinegar, astragalus root, lemon balm, turmeric, etc.

[121] In another embodiment of the present invention, examples of acid neutralizing compounds include potassium citrate, calcium carbonate, sodium lactate, calcium acetate, sodium bicarbonate, citric acid, magnesium hydroxide, aluminum hydroxide, etc.

[122] In another embodiment of the present invention, examples of anti-allergy compounds include alopatadine, astemizole, cromolyn, fenpiprane, repirinast, tranilast, traxanox, etc.

[123] In another embodiment of the present invention, examples of compounds that promote wound healing are N-acetylcysteine (NAC), dexpanthenol, and the like. See for example Oguz et al, Int Surg 2015, 100:656. A preferred liquid mucoadhesive composition formulated for use as a topical treatment of rectal mucositis contains from 0.1% to 5% of the wound healing compound, and more preferably contains either 3% NAC or 2.0-3.0% dexpanthenol.

[124] In another embodiment of the present invention, the amount of pharmaceutically active compound(s) to be used depends on the desired treatment strength, although preferably, the pharmaceutical component comprises 0.001 to 30% by weight of the formulation, and more preferably between 0.005 and 20% by weight.

[125] In addition to the preferred requirements of mucoadhesion as described above, it is important, for use of the composition for the prevention and treatment of mucosal diseases and disorders, and for use of the composition as a drug delivery vehicle, that the liquid, solid, semi-solid, gel, gummy or powder solution be stable, such that it can be stored at ambient temperatures for many months or years, even when subjected to brief periods of elevated or depressed temperatures, without significant physical or chemical degradation of the formulation. It is usually desirable to formulate the product without use of any organic solvents, the presence of which might irritate the mucosal lesions being treated. Furthermore, it is desirable to formulate the mucoadhesive solution using only excipients which are accepted by all major pharmaceutical regulating authorities as safe.

[126] A naturally occurring linear or cross-linked polymer polyanionic or polycationic polymer which may or may not already be known to provide mucoadhesion include (but are not limited to) carboxymethylcellulose, hydroxyalkylcellulose, dextran sulfate, dermatan sulfate, and hyaluronic acid. Other mucoadhesive polymers are well-known to those skilled in the art. The mucoadhesive formulations of the current invention can contain a single mucoadhesive component, or mixtures thereof. The preferred mucoadhesive polymer is sodium alginate. Viscosity enhancement is provided by one or more of the above mentioned mucoadhesive polymers alone or in combination with agar, bentonite, glycerin, povidone, kaolin, and/or tragacanth.

[127] In another embodiment of the present invention, the pH of the solution is adjusted to the final desired pH with any pharmaceutically accepted acid or base. Most preferred are sodium or potassium hydroxide, phosphoric acid, or citric acid. A final pH of 5.5 to 8.5 is preferred.

[128] In another embodiment of the present invention, to prevent microbial growth in the composition during storage, it is desirable to include a preservatives. Preservatives known in the art include benzyl alcohol, benzoate salts, phenoxyethanol, methylparaben, propylparaben, sorbitol and sorbic acid. Sorbic acid is the preferred preservative.

[129] In another embodiment of the present invention, a humectant is desirable to provide a pleasant mouth-feel in oral applications. Humectants known in the art include cholesterol, fatty acids, glycerin, lauric acid, magnesium stearate, pentaerythritol, propylene glycol, hyaluronic acid, honey, avocado oil, olive oil, cinnamon oil, coconut oil, emu oil, flaxseed oil, hemp oil, grape seed oil, jojoba, moringa oil, myrrh oil, frankincense oil, oregano oil, seabuckthorn oil, peppermint oil, spearmint oil, sunflower oil, tea tree oil, thyme essential oil, vitamin a, vitamin c, vitamin e etc. Glycerin is preferred.

[130] In another embodiment of the present invention, an emulsifying agent might be necessary, for example to ensure complete dissolution of all excipients, especially hydrophobic components such as hyaluronic acid. Many emulsifiers are known in the art. The preferred emulsifier is hyaluronic acid.

[131] In another embodiment of the present invention, for oral applications, it may be desirable to add a pharmaceutically acceptable flavoring agent and/or sweetener.

Compounds such as saccharin, glycerin, simple syrup, erythritol, sorbitol and xylitol are useful among those as sweeteners. Erythritol or Xylitol is preferred.

[132] In another embodiment of the present invention, it may be desirable to include other ingredients; for example a pharmaceutically acceptable organic solvent, a buffering agent, an antioxidant, an antimicrobial agent, acid-reducing and/or a coloring agent. The exact composition of the above ingredients, and the method of manufacture, will be apparent to those skilled in the art. A number of texts provide assistance in the design and manufacture of pharmaceutical formulations, including Remington's Pharmaceutical Sciences, Mack Publishing Company Co., Easton, Pa., and Pharmaceutical dosage forms and drug delivery, Ansel et al, 1995, Williams and Wilkins, Malvern, Pa.

Examples

[133] The following examples are presented to just a way to represent the invention, it should not be construed to limit the scope of the invention in any manner.

[134] The following examples provide preferred combinations of components of the stable, mucoadhesive liquid composition formulations of the current invention, set out below in Table 1 for the MucoPro System & RectaPro:

MUCOPRO STARTER		**MUCOPRO+**	
Purified Water	69.65	Purified Water	61.10
Glycerin	10.00	Glycerin	10.00
Witch Hazel	5.00	Witch Hazel	5.00
Honey	4.00	Lidocaine	4.00
Flavorant and Masking Agent	3.00	Honey	3.00
Olive Oil	2.50	Flavorant and Masking Agent	3.00
Sodium Alginate	1.80	Olive Oil	2.50
Beta Glucan (1, 3)	1.50	Sodium Aginate	1.80
Xylitol/Erythritol Natural Sweetner	1.50	Xylitol/Erythritol Natural Sweetner	1.75
Peppermint Oil	0.50	Dexpanthenol	1.50
Hyaluronic Acid	0.25	Glutamine	1.50
Sorbic Acid	0.20	Beta Glucan (1, 3)	1.50
Sodium Chloride	0.01	L-Lysine	0.50
Citric Acid	0.03	Tulsi	0.50
Aloe Vera	0.03	Peppermint Oil	0.50
Vitamin E	0.03	Hyaluronic Acid	0.50
	30.35	Ginger Extract	0.25
		L-Arginine	0.25
	100.00	L-citrulline	0.25

Menthol	0.25
Sorbic Acid	0.20
Sodium Chloride	0.01
Citric Acid	0.03
Aloe Vera	0.03
Vitamin A	0.03
Vitamin E	0.03
Cetrizine	0.01
Diphenhydramine hydrochloride	0.01

[135] The following examples provide additional preferred combinations of components of the stable, mucoadhesive liquid composition formulations of the current invention, set out below in Table 2 for the MucoPro System & RectaPro:

MUCOPRO ADVANCED

Purified Water	60.80
Glycerin	10.00
Witch Hazel	5.00
Lidocaine	4.00
Honey	3.00
Flavorant and Masking Agent	3.00
Olive Oil	2.50
Sodium Aginate	1.80
Xylitol/Erythritol Natural Sweetner	1.75
Dexpanthenol	1.50
Glutamine	1.50
Beta Glucan (1, 3)	1.50
L-Lysine	0.50
Tulsi	0.50
Peppermint Oil	0.50
Hyaluronic Acid	0.50
Fluconazole	0.30
Ginger Extract	0.25
L-Arginine	0.25
L-citrulline	0.25
Menthol	0.25
Sorbic Acid	0.20
Sodium Chloride	0.01
Citric Acid	0.03
Aloe Vera	0.03
Vitamin A	0.03
Vitamin E	0.03
Cetrizine	0.01
Diphenhydramine hydrochloride	0.01

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[135] The following examples provide additional preferred combinations of components of the stable, mucoadhesive liquid composition formulations of the current invention, set out below in Table 3 for the MucoPro System & RectaPro:

RECTAPRO		CBDPRO	
Purified Water	56.58	Purified Water	62.97
Glycerin	10.00	Glycerin	10.00
Witch Hazel	10.00	Flavorant and Masking Agent	4.00
Lidocaine	4.00	Witch Hazel	3.00
N-Acetyl L-Cysteine	3.00	Honey	3.00
Olive Oil	3.00	Olive Oil	3.00
Dexpanthenol	3.00	Peppermint Oil	3.00
Honey	2.00	Dexpanthenol	2.00
Glutamine	2.00	Lidocaine	2.00
Sodium Alginate	1.90	Xylitol/Erythritol Natural Sweetner	2.00
Beta Glucan	1.50	Beta Glucan (1, 3)	1.50
Menthol	1.00	Sodium Alginate	1.80
Tulsi	0.50	Hyaluronic Acid	0.50
Hyaluronic Acid	0.50	CBD Oil	0.40
L-Arginine	0.25	L-Arginine	0.25
L-citrulline	0.25	L-citrulline	0.25
Sorbic Acid	0.20	Sorbic Acid	0.20
Vitamin E	0.20	Sodium Chloride	0.01
Citric Acid	0.03	Citric Acid	0.03
Vitamin A	0.03	Aloe Vera	0.03
Aloe Vera	0.01	Vitamin A	0.03
Cetrizine	0.05	Vitamin E	0.03

[136] Various alternate embodiments are contemplated and readily determined using information and practices known to one skilled in the arts of the present inventions. References to published literature are cited to illustrate known applications, to provide enablement regarding the preferred concentrations of ingredients for a claimed mucoadhesive formulation, and the teachings of these references are hereby incorporated by reference.

What is claimed is:

1. An aqueous mucoadhesive and bioadhesive composition possessing antimicrobial and anti-inflammatory activities for the prevention and treatment of ulcerative, inflammatory and/or erosive disorders of mucous membranes comprising:

   a.) a mucoadhesive agent in an amount ranging from 0.01-10.0 wt %;

   b.) a bioadhesive agent in an amount ranging from 0.01-10.0 wt/wt %;

   c.) one or more pharmaceutically active agent in an amount ranging from (Kindly provide the range of wt%) which is therapeutically or prophylatically active against the mucocutaneous disorder;

   d.) one or more natural polymer ingredients in an amount ranging from 0.01-10.0 wt %; and

   e.) one or more cannabinoid in an amount ranging from 0.01-10% wt/wt along with pharmaceutically acceptable excipients.

2. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, the mucoadhesive agent is selected from agar, agarose, albumin, alginate, arame, bladderwrack, carrageenan, chitin, chitosan, collagen, dextran, dulse, gum Arabic, gelatin, guar gum, hyaluronic acid, hydroxyl propyl methyl cellulose, irish moss, lectin, manikara zapota, mastic gum, moringa gum, mytilus edulis, neem gum, nori, pectin, psyllium, sea palm, snail slime or mucus, sodium caroxymethylcellulose, soluble starch, sunflower lecithin, tamarind seed polysaccharide, tragacanth, xanthum gum or brown seaweed.

3. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, the bioadhesive agent is selected from plant lectins, nanohydroxapatite, β-defensin-3 peptide, salamander secretions, snail mucus, fenugreek gum, polysaccharides, fruit sugars, and dextran.

4. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, the pharmaceutically active agent is selected from anesthetic, analgesic, antihistamine, antiseptics, antioxidants, anti-fungals, antibacterials, anti-infectives, antiemetics, antidiarrheals, antifungals, anti-inflammatories, antimicrobial agents, astringents, cleansing agents, cooling agents, corticosteroids, emollients, flavorants,, flavonoids, healing agents, humectants, moisturizers, peptides, solubilizing agents, styptic agents, sweetners, vasodilators, provided said ingredient is present in an effective amount.

5. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, the natural polymer ingredient is selected from carboy methyl cellulose, hydroxy propyl methyl cellulose, Carbopol 934, Carbopol 971, Noveom AA, tragacanth, sodium alginate, polycarbophil, hydroxyl ethyl cellulose, and the like polymers.

6. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, the cannabinoid is selected from cannabidiol (CBD), tetrahydrocannabinol (THC), cannabidiolic acid (CBD-A), cannabigerolic acid (CBN-A), cannabigerol (CBG), cannabinolic acid (CBN-A), cannabichromenic acid (CBC-A), cannabichromene (CBC), and cannabinol (CBN).

7. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, the pharmaceutically active excipients are selected from the group consisting of cannabidiods, menthol, aspirin, acetaminophen, methyl salicylate, monoglycol salicylate, mefenamic acid, flufenamic acid, indomethacin, diclofenac, alclofenac, diclofenac sodium, ibuprofen, ketoprofen, pranoprofen, fenoprofen, sulindac, fenclofenac, clidanac, flurbiprofen, fentiazac, bufexarnac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, tiaramide hydrochloride, dextromethorphan, ibuprofen, naproxen, NSAIDS, cannabinioids, lidocaine, bupivacaine, benzocaine, butamben, carbamazepine, dibucaine, dibucaine, hydrochloride, ketamine, nupercainal, oxybuprocaine, pra-

moxine, prilocaine, proparacaine, proxymetacaine, tetracaine, cannabis sativa, phenylanaline, miconazole nitrate, fluconazole, nystatin, aclovir, chlorhexidine, clotrimazole, diflucan, candicidin, cetirizine, brompheniramine, chlorpheneramine maleate, clemastine, diphyenhydramine, fexofenadine, l-histidine, loratadine, witch hazel, boric acid, phenol, resorcinol, hydrastis, hydrogen peroxide, camphor, alpha lipoic acid, hydrastis, zinc oxide, tannic acid, dexamethasome, prelone, fluocinonide, clobetasol, halobeasol, hydrocortisone, praxmoxine hydrochloride, bismuth subsalicylate, clycopyrrolate, diphenoxlate-atropine, hyoscyamine sulfate ER, levsin elixir, lomotil, loperamide, motofen, simethicone, misoprostal, sucralafate, cholecalciferol, cyclizine hydrochloride, dimenhydramine hydrochloride, meclizine hydrochloride, aminoacetic acid, hyaluronic acid, bismuth oxide, bismuth subgallate, bismuth subnitrate, l-histidine, n-acetyl-l-cysteine, alopatadine, astemizole, cromolyn, fenpiprane, repirinast, tranilast, traxanox, salicylic acid, podophyllum resin, podolifox, cantharidin, chloroacetic acids and silver nitrate, testosterone, oxandrolone, diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride, chlorpheniramine maleate, isothipendyl hydrochloride, tripelennamine hydrochloride, promethazine hydrochloride, methdilazine hydrochloride, cetirizine, brompheniramine, clemastine, fexofenadine, loratadine, dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, p-buthylaminobenzoic acid 2-(die-ethylamino)ethyl ester hydrochloride, procaine hydrochloride, cetacean, oraqix, tetracaine, tetracaine hydrochloride, carbamazepine, dibucaine, dibucaine hydrochloride, chloroprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, piperocaine hydrochloride, dyclonine, dyclonine hydrochloride, bupivacaine, butamben, cannabanoids, carbamazepine, ketamine, nupercainal, oxybuprocaine, prilocaine, pramoxine, proparacaine, proxymetacaine, tetracaine, thimerosal, phenol, thymol, benzalkonium chloride, benzethonium chloride, chlorhexidine, povidone iodide, cetylpyridinium chloride, eugenol, miconazole nitrate, hydrogen peroxide, trimethylammonium bromide, naphazoline nitrate, tetrahydrazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tramazoline hydrochloride, hrombin, phytonadione, protamine sulfate, aminocaproic acid, tranexamic acid, carbazochrome, carbaxochrome sodium sulfanate, sulfamine, sulfathiazole, sulfadiazine, homosulfamine, sulfisoxazole, sulfisomidine, sulfamethizole, nitrofurazone, taxanes, platinum

compounds, topoisomerase I inhibitors, anthracycline, penicillin, meticillin, oxacillin, cefalotin, cefalordin, erythromeycin, lincomycin, tetracycline, chlortetracycline, oxytetracycline, metacycline, chloramphenicol, kanamycin, streptomycin, gentamicin, bacitracin, cycloserine, clindamycin, fungi zone, miconazole nitrate, nystatin, candicidin, fungizone, voriconazole, posaconazole, itraconazole, salicylic acid, podophyllum resin, podolifox, cantharidin. chloroacetic acids, silver nitrate, thymadine kinase inhibitors, sugar or glycoprotein synthesis inhibitors, structural protein synthesis inhibitors, attachment and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, ganciclovir, potassium citrate, calcium carbonate, sodium lactate, calcium acetate, sodium bicarbonate, citric acid, magnesium hydroxide, aluminum hydroxide, alopatadine, astemizole, cromolyn, fenpiprane, repirinast, tranilast, traxanox, Sarcandra glabra, Adenosine triphosphate (ATP), peppermint, peperine, licorice, glycyrrhiza, actobacillus acidophillis, lactobacillus bulgaricus, peppermint essential oil, willow bark powder, boswellia, curcumin, tulsi, cayenne, or turmeric extract or turmeric powder, bovine colostrum, cyclosporine A, hops, mustard oil, black cumin, turmeric, willow bark extract, wintergreen oil, myricetin, peppermint, cayenne, peperine, capsaicin, cloves, ashagandha extract, alphalipoic acid, african mango, phenylalanine, thuja, valerian, nigell sativa, mustard oil, cyclosporine A, tulsi, wintergreen, turmeric, curcumin, aloe vera, beta glucan 1, 3, honey, lemon extract, olive leaf extract, peppermint oil, sorbic acid, boswellia oil/extract, calendula, lactobacillus acidophilus, lemon extract, maitake, Manuka honey, lemongrass extract/oil, neem extract/oil, olive leaf, tea tree oil, turmeric, moringa seed extract, snail mucus, rutin, hesperidin, aloe vera, beta glucan 1,3, honey lemon extract , olive leaf extract, peppermint, sorbic acid, benzalkonium chloride solution, benzoic acid, , tea tree oil, black walnut, cinnamon, elecampane, garlic, oregano oil, l-histidine, melaleuca oil, mycology, olive leaf oil, rose oil, palmerosa oil, propolis, tulsi oil, menthol, pau d'arco tea, peppermint, lemon, petit grain oil, citronella oil, sage, elderberry, ginger, liquorice, oregano, green tea, apple cider vinegar, astragalus root, lemon balm, turmeric, etc.

8. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, the pH of the aforementioned composition is between 5.5-8.5.

9. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, said composition may be applied to mucosal membrane fir the delivery pf pharmaceutically active compounds to the mucosal membranes for the prevention and/or treatment of disorders or diseases of these membranes, for the delivery of pharmaceutically active compounds to systemic circulation by passage through the mucosal membrane.

10. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, said composition mat be applied to the oral, cavity, eyes, nasal cavity, rectal tissue, vagina, and /or the bladder.

11. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 wherein, said composition may be stable and applied in the form of mucoadhesive liquid, semi-solid, gel, gummy, solid and powder formulations.

12. A method for the treatment and/or prevention of ulcerative inflammation and/or erosive disorders of mucous membrane comprises the application of the aqueous composition as claimed in claim 1 to the mucosal membranes for the delivery of pharmaceutically active compounds.

13. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 and claim 12 wherein, the mucocutaneous disorder are several diseases, disorders and conditions of these mucosal surfaces which can result in severe pain, dryness of the buccal cavity, of the vaginal, nasal, intestinal, and eye, irritation, erythema, and/or ulceration. Examples of such diseases in the oral cavity include aphthous ulcers, bullous pemphigoid, oral lichen planus, stomatopharyngitis, in Sjogren's syndrome, oral mucositis, intestinal (nausea and vomiting), vaginal (e.g. vaginitis, bacterial vaginosis) and rectal mucositis, mucous membrane contact dermatitis, and inflammation and dryness of the eye (e.g. keratitis sicca,

conjunctivitis, dry eye disease, uveitis) examples of diseases of the nasal mucous membrane include sinusitis and rhinitis; an example for the bladder is interstitial cystitis. Certain diseases such as Behcet syndrome, can affect the mucocutaneous membranes of several regions of the body, many other ulcerative or inflammatory mucocutaneous diseases are known, including xerostomia, stomatitis (including caused by certain medications, appliances such as CPAP machines, etc.), and the like including painful ulcerative disorders of mucosal surfaces which result as an adverse side-effect in certain therapies, including certain medications treating various diseases such as rheumatoid arthritis, HIV, such as dental procedures and appliances, chemotherapy, radiation therapy or stem cell transplantation including mucositis, esophagitis, and radiation proctitis.

14. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 and claim 12 wherein, the dosage forms are compositions sufficiently used to coat a wide area of the mucosal surface, but are also bioadhesive and mucoadhesive useful to provide prolonged retention on the surface of the mucosa.

15. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 and claim 12 wherein, the composition when administered to the mucosal tissue, coats the mucosa to enhance and aid in the controlled release of pharmaceutically active agents.

16. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 and claim 12 wherein, said composition is substantially free of a synthetic polymer.

17. The aqueous mucoadhesive and bioadhesive composition as claimed in the claim 1 and claim 12 wherein, said composition contains at least 70% wt/wt of natural ingredients.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 2019/050971

A. CLASSIFICATION OF SUBJECT MATTER
(see extra sheet)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K 31/00, 45/08, 31/352, 31/717, 47/38, 47/36, A61P 31/00, 29/00,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSearch (RUPTO internal), USPTO, PAJ, Esp@cenet, DWPI, EAPATIS, PATENTSCOPE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/0228490 A1 (THE UNIVERSITY OF NORTH CAROLINAAT CHAPEL HILL) 11.08.2016, claims 98, 102, 108, [0006], [0008], [0015], [0016], [0293], [0298],[0299], [0310],[0326],[0180], [0182], [0194], [0252-0253], [0260], [0275], [0288], [0294],[0057], [0223], [0125], [0211], [0384], [0050], [0052], [0104], [0058], [0070], [0111], [0292],[0426]	1-17
A	WO 2006/103407A1 (OREXO AB) 05.10.2006	1-17
A	WO 2006/103418 A1 (OREXO AB) 05.10.2006	1-17

☐ Further documents are listed in the continuation of Box C.
☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2019 (21.05.2019)	30 May 2019 (30.05.2019)
Name and mailing address of the ISA/RU: Federal Institute of Industrial Property, Berezhkovskaya nab., 30-1, Moscow, G-59, GSP-3, Russia, 125993 Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37	Authorized officer V. Temnova Telephone No. 8 499 240 25 91

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INTERNATIONAL SEARCH REPORT
Classification of subject matter

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A61K 45/08 *(2006.01)*
A61K 47/36 *(2006.01)*
A61K 31/352 *(2006.01)*
A61K 47/38 *(2006.01)*
A61P 31/00 *(2006.01)*
A61P 29/00 *(2006.01)*