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(71) Applicant: **RUBICON RESEARCH PRIVATE LIMITED** [IN/IN]; 221, Annexe Building, Goregaon Mulund Link Road, Opposite Indira Container Yard, Off L.B.S. Marg, Bhandup (West), Mumbai 400078 (IN).

(72) Inventors: **PILGAONKAR, Pratibha Sudhir**; Rubicon Research Private Limited, 221, Annexe Building, Goregaon Mulund Link Road, Opposite, Indira Container Yard, Off L.B.S. Marg, Bhandup (West), Mumbai 400078 (IN). **RUSTOMJEE, Maharukh Tehmasp**; Rubicon Research Private Limited, 221, Annexe Building, Goregaon Mulund Link Road, Opposite, Indira Container Yard, Off L.B.S. Marg, Bhandup (West) Mumbai 400078 (IN). **GANDHI, Anilkumar Surendrakumar**; Rubicon Research Private Limited, 221, Annexe Building, Goregaon Mulund Link Road, Opposite, Indira Container Yard, Off L.B.S. Marg, Bhandup (West), Mumbai 400078 (IN).

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(54) Title: FORMULATIONS FOR MUCOSAL ADMINISTRATION

(57) Abstract: The present invention discloses formulations for mucosal administration comprising fenugreek fiber based excipient. The present invention further relates to formulations suitable for administration to nasal, buccal, sublingual, gingival, pulmonary, rectal, or vaginal mucosae.

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FORMULATIONS FOR MUCOSAL ADMINISTRATION

Field of the Invention

The present invention relates to formulations for mucosal administration comprising fenugreek fiber based excipient. Particularly the present invention relates to formulations suitable for administration to nasal, buccal, sublingual, gingival, pulmonary, rectal, or vaginal mucosae. The present invention also provides processes for preparing such formulations and methods of using such formulations.

Background of the Invention

Amongst the various routes of drug delivery, the oral route is perhaps the most preferred by patients and clinicians. However peroral administration of drugs has disadvantages, such as hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract, which reduces the efficacy of oral administration of drugs. Consequently other absorptive mucosae are considered as potential sites for drug administration. Several mucosal surfaces have been investigated as delivery routes including nasal, oral, pulmonary, rectal and vaginal. These mucosal routes of drug delivery offer distinct advantages over peroral administration for systemic or local effect. These advantages include bypass of first pass effect, avoidance of presystemic elimination of the drug within the gastrointestinal tract, noninvasive administration and if required, delivery of drugs directly into systemic circulation.

Mucosal administration has been used successfully for the delivery of a number of therapeutic and/or beneficial agents, on and/or into and/or across the mucosa including nasal, oral, pulmonary, rectal or vaginal. However, the mucosal surface as a site for administration of pharmaceutical formulations for preventive, therapeutic or other beneficial effect has limitations as well. The mucosal membranes, depending on their functionality, have a specific cellular physiology and can therefore variably present physiological barriers such as pH of the milieu, available absorptive surface area, permeability of the mucosa, texture of the membrane, clearance mechanism, proteolytic enzymes present in and around the mucosal region. These factors along with the physico-chemical properties of drugs and other biomolecules or agents to be delivered and the local or systemic effect desired, need to be considered while designing a formulation for mucosal administration.

The nasal mucosa for instance is considered to be promising for delivery of many drugs, proteins and other large biomolecules and has reached commercial status with several drugs. The nasal cavity is easily accessible, and extensively vascularized, however, certain limiting factors such as rapid mucociliary clearance, enzymatic degradation in the mucus layer and nasal epithelium, and low permeability of the nasal epithelium present significant barrier to retention of the dosage form at the site of action or drug absorption. Similar to the nasal route, the oral cavity as a site for mucosal administration has also achieved commercial success with several drugs. The oral mucosa is easily accessible, relatively permeable, highly vascularized, has minimal proteolytic activity and provides more hydrated environment for solubilisation of drugs. Within the oral cavity the common regions for mucosal delivery for local action or systemic absorption are the sublingual mucosa, labial mucosa and the buccal mucosa and selecting one over the others is mainly based on the anatomical and permeability properties of the sites, the desired residence time, and the desired effects of the drug or beneficial agent being administered. These oral mucosal routes also have the advantages of rapid onset of action, non-invasive administration, improved bioavailability of certain drugs and better patient compliance. However, the performance of the dosage form at the oral mucosa for delivery of therapeutic and/or beneficial agents, on and/or into and/or across the mucosa may be variable. Various factors including low residence time at the application site, high variability in bioavailability due to salivary secretion and oral musculature activity can also decrease the efficiency of systemic absorption from the oral cavity or local action at the site of administration.

Further, mucosal delivery at and/or across the pulmonary mucosa also provides a number of advantages. The lungs represent a high surface area through which drugs can be absorbed. The lung tissues are also relatively permeable. However, mucociliary transport in the airways causing decreased drug residence time, drug metabolism in the respiratory tract and reduction of systemic effect are some drawbacks associated with pulmonary delivery of active agents. Medications may be administered by the rectal mucosal route for local or systemic effects. Rectal administration also provides rapid absorption of many drugs and may be an easy alternative to the intravenous route. However various factors including pH of the rectal contents, rectal retention of drug(s) or dosage forms administered, reduced patient compliance and differences in venous drainage within the rectosigmoid region may affect efficiency of drug delivery via this

route. Further the large surface area, rich blood supply and permeability to a wide range of compounds including peptides and proteins make the vaginal mucosa too suitable for local or systemic drug administration. However variations in vaginal pH and secretions, low convenience, or reduced residence of the dosage form may affect the absorption and bioavailability of drugs being delivered by the vaginal route.

A major limitation therefore in general of the various routes of mucosal administration is the lack of dosage form retention at the site of local action and/or absorption. For significant drug absorption to occur or for desired local effect to occur, the drug and/or dosage form must have a prolonged exposure to the mucosal surface. Various formulation strategies including use of bioadhesive agents, viscosity enhancers, or gelling agents have been investigated to overcome this limitation and improve the residence time, absorption and/or bioavailability of the active agent delivered and/or the efficacy and performance of the dosage form administered.

Viscosity modulators, gelling agents and bioadhesives, cause effective deposition of the formulation at the mucosal site of absorption or local action, prolong mucosal residence or retention time of the dosage form, minimize drug loss from mucosal absorption site, promote absorption and/or permeability and eventually improve the bioavailability of the active and efficacy of the dosage form. Viscosity and/or mucoadhesion thus influence the overall performance of the formulations or dosage forms for mucosal administration. Additionally use of viscosifying or gelling agents cause accurate dosing of the active. The incorporation of viscosity modulators and/or gelling agents and/or bioadhesives, modifies the effect of mucociliary clearance and maintains the delivery system at a particular location for desired period of time.

Polymers are commonly added to the compositions for mucosal administration to increase the viscosity of the formulations and/or impart gelling and/or mucoadhesive properties to the same resulting in enhancement of absorption and/or localized action and/or bioavailability of the active. Synthetic hydrophilic polymers such as cellulose based polymers like carboxymethyl cellulose, hydroxy methylcellulose, hydroxypropyl methylcellulose or polyalcohols like polyvinyl alcohol or polyacrylic acids such as carbomers, polycarbophil and like are commonly used in formulations for mucosal administration. Natural polysaccharides such as hyaluronic acid, guar gum, alginates,

tragacanth, xylloglucan gum, chitosan, gellan gum, pectin etc. have also been used in formulations for mucosal administration. However, the use of some of these polymers have been found to increase residence time of a drug or a dosage form at the mucosal sites of absorption and/or localized action to a limited extent and has lead to only modest improvement in effectiveness of the formulation or dosage form and/or absorption and bioavailability of the active agent, requiring application of the same formulation to the site of action or absorption multiple times to achieve the intended therapeutic or desired effect which in turn affects the patient compliance. Furthermore some of these polymers are expensive too and may increase the overall cost of the formulation. Some also exhibit variable viscosity building and/or gelling and/or bioadhesive properties resulting in undesirable performance or changes in the formulations for mucosal administration or some interact with the active agents or other excipients in the compositions.

A need therefore exists to employ an excipient in the formulations for mucosal administration that is biocompatible, has excellent viscosity modulation and bioadhesive properties, is compatible with active agents and other excipients commonly employed in the mucosal formulations, improves residence time or contact of the formulation at the mucosal site of action as desired, is economical, and does not exhibit any adverse effect including damage to the mucosae.

The present inventors after thorough research provide formulations for mucosal administration comprising fenugreek fiber based excipient obtained from fenugreek seeds. The fenugreek fiber based excipient employed is a simple, economical, biocompatible excipient obtained from a natural source. Rigorous experimental studies have shown that the fenugreek fiber based excipient has viscosity, hydrating and gelling properties desirable for use in mucosal formulations. Moreover the fenugreek fiber based excipient has bioadhesive properties that can aid improving the residence time of the mucosal formulation at the mucosal site of action and/or absorption. Further the fenugreek fiber based excipient is stable and compatible with active agents and other excipients employed in formulations. The fenugreek fiber based excipient does not exhibit adverse effects.

Fenugreek fiber based excipient comprising fenugreek dietary fibers, such as, but not limited to, soluble dietary fibers, insoluble dietary fibers or combinations thereof can be

employed in mucosal formulations in accordance with the present invention. Exemplary fenugreek fiber based excipient comprising fenugreek fibers with soluble and insoluble dietary fibers and processes for preparation thereof have been described in European Patent 1697050B1 and PCT Publication WO2011/124973A1, entire contents of which have been incorporated herein by reference.

Summary of the Invention

The present invention relates to formulations for mucosal administration comprising fenugreek fiber based excipient. The present invention discloses formulations comprising fenugreek fiber based excipient suitable for administration to nasal, buccal, sublingual, gingival, pulmonary, rectal, or vaginal mucosae.

Detailed Description of the Invention

The present invention provides a formulation for mucosal administration comprising fenugreek fiber based excipient and at least one pharmaceutically acceptable excipient.

The term "mucosal", unless specified otherwise, refers to a tissue comprising a mucous membrane, such as, but not limited to, nasal mucosa, pulmonary mucosa, oral mucosa (including sublingual, buccal, gingival, palatal), rectal or vaginal mucosa. The term "mucosal administration", unless specified otherwise, means administration of a formulation or dosage form to a mucosal membrane for action on the mucosa and/or in the mucosa and/or absorption into the mucosa and/or across the mucosa (transmucosally) thereby providing desired local or systemic effect. Examples include, but are not limited to, buccal, sublingual, nasal, vaginal, pulmonary, gingival, palatal and rectal mucosal membranes. The term "mucosal formulation/s", unless specified otherwise, refers to formulations for administration to a mucosal membrane for action on the mucosa and/or in the mucosa and/or absorption into the mucosa and/or across the mucosa (tranmucosally) thereby providing desired local or systemic effect.

For the purpose of the present invention the term "active" or "active agent" or "beneficial agent" means any substance natural or synthetic which induces a pharmacological or biological effect in a subject. Such substances are intended to furnish biological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

In one embodiment the mucosal formulations of the present invention are suitable for drug or active agent delivery for local or systemic effect. In a further embodiment, the formulations of the present invention for mucosal administration comprise at least one active, fenugreek fiber based excipient and at least one pharmaceutically acceptable excipient. In another embodiment, the mucosal formulation of the present invention can be employed to deliver one or more active agent/s. Non limiting examples of active agents that may be delivered by the compositions of the present invention include, anti-inflammatory agents, calcium or potassium channel antagonists, β-adrenergic agonists, vasodilators, COX-1 and/or COX-2 inhibitors, antibacterial, antiviral, antipsychotic, antifungal, anti-osteoporotic, anti-migraine, anti-HIV, anti-cancer agents and the like or combinations thereof. Non-limiting examples of active agents that may be delivered by the formulations of the present invention include, but are not limited to, aspirin, ibuprofen, indomethacin, phenylbutazone, bromfenac, fenamate, sulindac, nabumetone, ketorolac, naproxen, diltiazem, israpidine, nimodipine, felodipine, verapamil, nifedipine, nicardipine, bepridil, dofetilide, almokalant, sematilide, ambasilide, azimilide, tedisamil, azelastine, beclometasone, budesonide, levocabastine, mometasone, olapatadine, sodium cromoglicate, triamcinolone acetonide, mupirocin, estradiol, nicotine, cyanocobalamin, desmopressin, buserelin, nafarelin, fentanyl, butorphanol, sotalol, piroxicam, ibutilide, terbutaline, salbutamol, metaproterenol, and ritodrine, nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, naproxen, ketoprofen, ketorolac, indomethacin, buprinorphine, prochloperazine, doxycycline, amikacin, gentamycin, diclofenac, tenoxicam, celecoxib, meloxicam, flosulide, alendronate, clodronate, etidronate, pamidronate, tiludronate, ibandronate, zoledronate, olpadronate, residronate and neridronate, miconazole, terconazole, isoconazole, fenticonazole, fluconazole, nystatin, ketoconazole, clotrimazole, butoconazole, econazole, metronidazole, ondansetron, domperidone, clonazepam, valproic acid, clobazam, lorazepam, nimodipine, nobiletin, tacrine, diazepam, raltitrexe, sildenafil citrate, midazolam, clindamycin, 5-fluoracil, acyclovir, AZT, famovir, ribavirin, penicillin, tetracycline, erythromycin, almotriptan, eletriptan, flovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, ergotamine, dihydroergotamine, bosentan, lanepitant., vincristine, cisplastin, doxorubicin, daunorubicin, etoposide, topotecan, irinotecan, paclitaxel, docetaxel, cyclophosphamide, methotrexate, gemcitabine, saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, lopinavir, ganciclovir, insulin, calcitonin, vasopressin, luprolide, somatostatin, oxytocin,

bivalirudin, integrilin, natrecor, abarelix, gastrine G17, peptide, ziconotide, cereport, interleukin, humanized antibodies, growth hormone and the like or combinations thereof suitable for mucosal administration. Active agents in the form of free acid or free base or pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts, pharmaceutically acceptable salts of prodrugs, active metabolites, polymorphs, solvates, hydrates, enantiomers, optical isomers, tautomers or racemic mixtures thereof can be employed in the formulations of the present invention for mucosal administration. In one embodiment one or more active agents within any dose range can be delivered with the mucosal formulations of the present invention comprising fenugreek fiber based excipient. In a further embodiment one or more active agents within any water solubility range can be delivered with the formulations of the present invention for mucosal administration comprising fenugreek fiber based excipient.

Fenugreek fiber based excipient isolated from seeds of Fenugreek or *Trigonella foenum-graceum* is employed in mucosal formulations of the present invention. Fenugreek or *Trigonella foenum-graceum* is an herbaceous plant of the leguminous family and is one of the oldest cultivated plants and through the ages has found wide applications as a food, a food additive and as a traditional medicine in every region where it has been cultivated.

The term "fenugreek fiber based excipient" as used in the present invention refers to an excipient obtained from fenugreek or *Trigonella foenum-graceum* seeds comprising fenugreek dietary fibers such as either soluble fenugreek dietary fibers, insoluble fenugreek dietary fibers or any combinations thereof. In a further embodiment "fenugreek fiber based excipient" as used in the present invention refers to an excipient obtained from fenugreek or *Trigonella foenum-graceum* seeds comprising at least about 30% by weight of fenugreek dietary fibers such as either soluble fenugreek dietary fibers, insoluble fenugreek dietary fibers or any combinations thereof. The soluble fenugreek dietary fiber that may be present in the fenugreek fiber based excipient includes, but is not limited to, fenugreek galactomannans. The insoluble fenugreek dietary fibers that may be present in the fenugreek fiber based excipient includes, but is not limited to, cellulose, hemicellulose, lignin and the like or any combinations thereof.

In one embodiment the fenugreek fiber based excipient employed in the composition of the present invention has a viscosity of at least 10,000 cps at 2%w/v at 25°C. In a further embodiment the fenugreek fiber based excipient employed in the composition of the present invention has a viscosity of at least 50,000 cps at 2%w/v at 25°C. In another embodiment the fenugreek fiber based excipient employed in the composition of the present invention has a protein content of not more than about 10% by weight of the fiber based excipient. In a further embodiment the fenugreek fiber based excipient employed in the composition of the present invention is substantially free of 4-hydroxyisoleucine, saponins and alkaloids. The term "substantially free" as used herein means the fenugreek fiber based excipient employed in the compositions of the present invention contain not more than 1% by weight, preferably not more than 0.4% of 4-hydroxyisoleucine, not more than 5%, preferably not more than 1%, more preferably not more than 0.5% of alkaloids such as trigonelline and not more than 5%, preferably not more than 1%, more preferably not more than 0.5% of saponins such as diosgenin.

The fenugreek fiber based excipient may be present in the compositions of the present invention in an amount of about 0.01% to about 99% by weight of the formulation of the present invention.

In one embodiment, the fenugreek fiber based excipient employed in the formulations of the present invention for mucosal administration comprises soluble dietary fibers and insoluble dietary fibers. In a further embodiment, the fenugreek fiber based excipient employed in the formulations of the present invention for mucosal administration comprises soluble dietary fibers and insoluble dietary fibers wherein the total dietary fibers including soluble and insoluble dietary fibers are present in an amount of about at least 30% by weight of the fenugreek fiber based excipient. In another embodiment, the fenugreek fiber based excipient employed in the mucosal formulation of the present invention comprises soluble dietary fibers and insoluble dietary fibers wherein the total dietary fibers are present in an amount of about at least 50% by weight of the fenugreek fiber based excipient. In a further embodiment, the fenugreek fiber based excipient employed in the mucosal formulation of the present invention comprises soluble dietary fibers and insoluble dietary fibers wherein the total dietary fibers are present in an amount of about at least 75% by weight of the fenugreek fiber based excipient. In another embodiment, the fenugreek fiber based excipient employed in the mucosal

formulation of the present invention comprises soluble dietary fibers and insoluble dietary fibers wherein the total dietary fibers are present in an amount of about at least 85% by weight of the fenugreek fiber based excipient. In a further embodiment, the fenugreek fiber based excipient employed in the mucosal formulation of the present invention comprises soluble dietary fibers and insoluble dietary fibers wherein the total dietary fibers are present in an amount of about at least 90% by weight of the fenugreek fiber based excipient. In another embodiment, the fenugreek fiber based excipient employed in the mucosal formulation of the present invention comprises soluble dietary fibers and insoluble dietary fibers wherein the total dietary fibers are present in an amount of about at least 95% by weight of the fenugreek fiber based excipient.

In one embodiment of the present invention, the fenugreek fiber based excipient when comprising soluble and insoluble dietary fibers the ratio of insoluble dietary fiber to soluble dietary fiber in the fenugreek fiber based excipient is about 0.05 to about 5. In another embodiment of the present invention, this ratio of insoluble dietary fiber to soluble dietary fiber is about 0.1 to about 4. In further embodiment of the present invention; this ratio of insoluble dietary fiber to soluble dietary fiber is about 0.5 to about 4. In another embodiment of the present invention, this ratio of insoluble dietary fiber to soluble dietary fiber is about 0.8 to 3. In yet another embodiment, this ratio of insoluble dietary fiber to soluble dietary fibers is about 1 to about 3. In a further embodiment, this ratio of insoluble dietary fiber to soluble dietary fibers is about 0.05 to about 1. In another embodiment, this ratio of insoluble dietary fiber to soluble dietary fibers is about 0.075 to about 0.8. In a further embodiment, this ratio of insoluble dietary fiber to soluble dietary fibers is about 0.1 to about 0.6. In a further embodiment, fenugreek fibers can be incorporated in the compositions of the present invention in any suitable form not restricted to powder and granules.

Without being bound by any theory it is believed that the fenugreek fiber based excipient employed in the present invention provides desired viscosity to the formulations of the present invention for mucosal administration. The fenugreek fiber based excipient has bioadhesive property that helps provide formulations for mucosal administration with desired residence time at the mucosal site of action and/or absorption. The fenugreek fiber based excipient also has gelling and hydrating ability making it suitable for use in different mucosal formulations.

In a further embodiment, the formulations of the present invention for mucosal administration can be in the form of different dosage forms depending on the route of administration. Non-limiting examples of dosage forms for sublingual, buccal, gingival, palatal, nasal, rectal, vaginal administration or any other routes of mucosal administration include, but are not limited to, tablets, pellets, powders, sprays, quick dissolve tablets, lozenges, patches, ointments, gels, gargles, jellies, aerosols, foams, pumps, films, microemulsions, creams, lotions, pastes, solutions, suspensions, suppositories, and the like. In one embodiment, the formulations of the present invention are in the form of mucoadhesive dosage forms. In another embodiment, the formulations of the present invention may be a particulate delivery system, such as, but not limited to, liposomes, nanoparticles, microparticles, microspheres and the like. The state of the medicament of the present invention is not particularly limited and it may be in an arbitrary state such as solid semisolid liquid and gel. The dosage form of the present invention may be in the form, such as but not limited to solid, semisolid or liquid.

In a further embodiment the formulations of the present invention may be employed for local effect. In one embodiment, the formulations of the present invention are for action on the mucosa and/or in the mucosa. In another embodiment, the formulations of the present invention are employed for systemic effect. In another embodiment, the formulations of the present invention are for delivery of the active agent across the mucosa.

The mucosal formulations depending on the dosage form and the route of mucosal administration further comprise at least one pharmaceutically acceptable excipient. Suitable pharmaceutically acceptable excipients that may be employed include, but are not limited to, diluents, binders, lubricants, glidants, sweetening and flavoring agents, preservatives, disintegrants, penetration enhancers, demulcents, tonicity adjusting agents, buffering agents, pH adjusting agents, solubilizing agents, surfactants, chelating agents, emulsifying agents, suspending agents, stabilizers, antioxidants, release controlling agents, carriers, plasticizers, and the like or combinations thereof.

Examples of suitable binders include, but are not limited to, starch, pregelatinized starch, polyvinyl pyrrolidone, copovidone, cellulose derivatives, such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose and their salts, and the like or

combinations thereof. Examples of suitable diluents include, but are not limited to, starch, microcrystalline cellulose, lactose, xylitol, mannitol, maltose, polyols, fructose, guar gum, sorbitol, magnesium hydroxide, dicalcium phosphate, and the like or any combinations thereof. Examples of disintegrants include, but are not limited to, natural, modified or pregelatinized starch, crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose, calcium silicate, effervescent disintegrating systems and the like or combinations thereof. Effervescent disintegrating systems include, but are not limited to, thermolabile gas generating agents such as, but not limited to, sodium bicarbonate, sodium glycine carbonate, potassium bicarbonate, ammonium bicarbonate, sodium bisulfite, sodium metabisulfite, and the like or combinations, and an acid source such as, but not limited to, citric acid, maleic acid, tartaric acid and the like or combinations thereof. Suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, talc, sodium stearyl fumarate, and the like or combinations thereof. Suitable glidants that may be employed include, but are not limited to, colloidal silica, silica gel, precipitated silica, and the like or combinations thereof. Suitable stabilizers that may be employed include, but not limited to, benzoic acid, sodium benzoate, citric acid, and the like or combinations thereof. Souring agents include, but are not limited to, monosodium fumarate and/or citric acid. Suitable sweeteners include, but are not limited to, aspartame, stevia extract, glycyrrhiza, saccharine, saccharine sodium, acesulfame, sucralose and dipotassium glycyrrhizinate and the like or combinations thereof. Suitable flavors include, but are not limited to, mint flavour, orange flavour, lemon flavor, strawberry aroma, vanilla flavour, raspberry aroma, cherry flavor, tutty frutty flavor, magnasweet 135, key lime flavor, grape flavor, trusil art 511815, fruit extracts and the like or combinations thereof.

Suitable demulcents include, but are not limited to, glycerin, polyvinyl pyrrolidone, polyethylene oxide, polyethylene glycol, propylene glycol, sorbitol and polyacrylic acid and the like or combinations thereof. Chelating agents may include, but are not limited to, EDTA and its salts. Tonicity adjusting agents useful in the compositions of the present invention may include, but are not limited to, salts such as, but not limited to, sodium chloride, potassium chloride and calcium chloride, non-ionic tonicity agents may include, but are not limited to, propylene glycol, glycerol, mannitol, dextran and the like or combinations thereof. pH adjusting agents may include sodium hydroxide, hydrochloric acid, boric acid, Tris, triethanolamine and sodium hydroxide. Suitable buffering agents

include, but are not limited to, phosphates, acetates and the like, and amino alcohols such as 2-amino-2-methyl-1-propanol (AMP), ascorbates, borates, hydrogen carbonate/carbonates, citrates, gluconates, lactates, propionates and TRIS (tromethamine) buffers, and the like or combinations thereof. Suitable preservatives include, but are not limited to, benzalkonium chloride, polyquaternium-1, p-hydroxybenzoic acid ester, sodium perborate, sodium chlorite, alcohols such as chlorobutanol, benzyl alcohol or phenyl ethanol, guanidine derivatives such as polyhexamethylene biguanide, sodium perborate, sorbic acid, and the like or combinations thereof. Suitable solubilizers include, but are not limited to cetostearyl alcohol, cholesterol, diethanolamine, ethyl oleate, ethylene glycol palmitostearate, glycerin, glyceryl monostearate, isopropyl myristate, lecithin, medium-chain glyceride, monoethanolamine, oleic acid, propylene glycol, polyoxyethylene alkyl ether, polyoxyethylene castor oil glycoside, polyethylene sorbitan fatty acid ester, polyoxyethylene stearate, propylene glycol alginate, sorbitan fatty acid ester, stearic acid, sunflower oil, triethanolmine, polyoxyl 40 hydrogenated castor oil, tween 80, cyclodextrin and mixtures thereof. Suitable penetration enhancers that may optionally be employed include, but are not limited to, polyoxyethylene glycol stearyl ether, polyoxyethylene glycol oleyl ether, polyoxyethylene glycol lauryl ether, sodium glycol deoxycholate, sodium taurocholate, sodium deoxycholate, sodium glycocholate, saponins, and the like or combinations thereof. Suitable surfactants that may be employed include, but are not limited to, ionic, amphiphilic or nonionic surfactants, and the like or combinations thereof. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, or polypeptides; glyceride derivatives of amino acids; lecithins or hydrogenated lecithins; lysolecithins or hydrogenated lysolecithins; phospholipids or derivatives thereof; lysophospholipids or derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- or di-acetylated tartaric acid esters of mono- or di-glycerides; succinylated mono- or di-glycerides; citric acid esters of mono- or di-glycerides; and the like or mixtures thereof. Suitable amphiphilic surfactants include, but are not limited to, d-α-tocopheryl polyethylene glycol 1000 succinate and d-α-tocopherol acid salts such as succinate, acetate, and the like or combinations thereof. Suitable non-ionic surfactants include, but are not limited to, fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty

acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols or sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- or di-glycerides; oil-soluble vitamins/vitamin derivatives; PEG fatty acid esters; polyglycerized fatty acid; polyoxyethylene-polyoxypropylene block copolymers; transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols wherein the commonly used oils are castor oil or hydrogenated castor oil, or an edible vegetable oil such as corn oil, olive oil, peanut oil, palm kernel oil, almond oil and the commonly used polyols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol and pentaerythritol; or mixtures thereof. Suitable surfactants may be employed as emulsifying agents.

Antioxidants such as, but not limited to, ascorbic acid, acetylcysteine, cysteine, sodium hydrogen sulfite, butylated hydroxyanisole, butylated hydroxytoluene or alpha-tocopherol acetate may be employed. Suitable pharmaceutical carriers include water; electrolytes such as sodium chloride; saline; lower alkanols, glycols, polyols, ointment bases such as but not limited to, natural wax, petroleum wax, and the like or combinations thereof. Release controlling excipients, such as but not limited to, polymeric release controlling excipients, non-polymeric release controlling excipients or combinations thereof may be included in the compositions of the present invention. Exemplary polymeric release controlling excipients include, but are not limited to, polyvinyl acetate, mixture of polyvinyl acetate and polyvinylpyrrolidone, polymethacrylic acid derivatives, cellulose derivatives, acrylic acid derivatives, maleic acid copolymers, polyvinyl derivatives, and combinations thereof. Exemplary non-polymeric release controlling excipients include, but are not limited to, fatty acids, long chain alcohols, fats and oils, waxes, phospholipids, eicosonoids, terpenes, steroids, resins and the like or combinations thereof. In one embodiment, fenugreek fiber based excipient can also be used as a release controlling agent. Suitable plasticizers include, but are not limited to, triethyl citrate, dibutylphthalate, diethylphthalate, acetyltriethyl citrate, tributyl citrate, acetyltetrabutyl citrate, triacetin, polyethylene glycol, castor oil, and the like or combinations thereof.

The formulations of the present invention for mucosal administration may optionally include additional viscosity enhancing agents such as, but not limited to, cellulose and cellulose derivatives, such as, but not limited to, methylcellulose, hydroxypropylcellulose,

hydroxyethyl cellulose, ethylhydroxyethyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, cellulose acetophthalate, and the like or combinations thereof; alginic acid, sodium alginate, propylene glycol alginate, polyvinylpyrrolidone, carboxyvinyl polymers or carbomers (Carbopol®), polyvinyl alcohol, glycerin, polyethylene glycol, triblock copolymers of polyoxypropylene and polyoxyethylene, polyethoxylated sorbitan, polysorbate 80, chondroitin sulfate, dimethicone, perfluorononyl dimethicone, cyclomethicone, dextrans, proteoglycans, natural polysaccharides, such as, but not limited to, hyaluronic acid and salts thereof, guar gum, karaya, xyloglucan gum, chitosan, gellan gum, pectin, collagen, modified collagen and like or combinations thereof.

The formulations of the present invention for mucosal administration may optionally include additional gelling agents such as, but not limited to, polysaccharide gums such as, but not limited to, gellan gum, tamarind gum, tragacanth, locust bean gum, agarose, carageenans, guar gum, hydroxypropyl guar gum, hyaluronic acid, chitosan, konjac, acacia, pectin, arabic, curdlan, glucan gum, scleroglucan and sulfated glucan sulfate and the like or combinations thereof; cellulose and its derivatives such as, but not limited to, methyl cellulose, carboxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, methyl hydroxypropyl cellulose, hydroxypropyl methyl cellulose, cellulose acetate, ethyl cellulose, methyl hydroxyethyl cellulose, hydroxyethyl cellulose, cellulose gum, and the like or combinations thereof; cross-linked acrylic polymers or carbomer (Carbopol^{TM}), aloe vera gel, polyvinyl alcohol, polyacrylamide, poloxamer, polymethylvinylether-maleic anhydride, swellable water-insoluble polymers such as, but not limited to, hydrogel and the like or combinations thereof. Ion exchange resins such as, but not limited to, inorganic zeolites or synthetically produced organic resins may be employed in the compositions of the present invention.

The formulations of the present invention for mucosal administration may optionally include additional mucodhesive agents such as, but not limited to, polyacrylic acid, hyaluronans, chitosan, pullulan, cellulose derivatives such as, but not limited to, methyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethylcellulose, poly (galacturonic) acid, sodium alginate, pectin, xyloglucan, xanthan gum, carbomers (Carbopol^{TM}), polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, poloxamer, and the like or combinations thereof.

In a further embodiment, the formulation of the present invention can be in the form of an oral patch, comprising a water insoluble or slowly soluble support layer and an adhesive layer showing adhesion to mucosa and laminated on the support.

The adhesive layer has a function of adhering and fixing the pharmaceutical composition to the oral mucosa and the active ingredient added to this adhesive layer is dissolved out of the adhesive layer and reaches the oral mucosal surface for local action or systemic absorption. Such an adhesive layer may comprise fenugreek fiber based excipient. The water insoluble support layer has a function of protecting the pharmaceutical composition from the saliva as well as water drink or food to be contained in the mouth. The water insoluble or slowly soluble support layer may comprise substances, such as but not limited to, ethylcellulose hydroxyethylcellulose hydroxypropylmethylcellulose phthalate hydroxypropylmethylcellulose acetate succinate cellulose acetate phthalate shellac polyisobutylene and polyisoprene. In addition to the aforementioned form of two laminated layers the aforementioned pharmaceutical composition may be a pharmaceutical composition comprising three or more laminated layers by adopting two or more layers for either one or both of the aforementioned layers.

The above listing of excipients is given for illustrative purposes and is not intended to be exhaustive. Examples of other agents useful for the foregoing purposes are well known to a person skilled in the art and are contemplated by the present invention. It is also contemplated that the concentrations of the excipients in the formulations of the present invention can vary.

In one embodiment, the formulations of the present invention for mucosal administration release the active agent or beneficial agent immediately for local or systemic action. In another embodiment, the formulations of the present invention for mucosal administration are for sustained or controlled release of active agent or beneficial agent at the site of mucosal administration for local or systemic action. In yet another, embodiment, the formulations of the present invention for mucosal administration can release one active immediately after administration and the same or different active in a sustained or controlled manner. In a further embodiment, the mucosal formulations of the present invention are for once-a-day administration. In one embodiment, the sustained or

controlled release delivery of the active agent from the mucosal formulation is for a sustained period of time of about 24 hours. In another embodiment, the sustained or controlled release delivery of the active agent from the mucosal formulation is for a sustained period of time of about 12 hours. In a further embodiment, the sustained or controlled release delivery of the active agent from the mucosal formulation is for a sustained period of time of about 10 hours. In yet another embodiment, the sustained or controlled release delivery of the active agent from the mucosal formulation is for a sustained period of time of about 8 hours. In one embodiment, the sustained or controlled release delivery of the active agent from the mucosal formulation is for a sustained period of time of about 6 hours. In a further embodiment, the mucosal formulations of the present invention may be for moisturizing the mucosal membrane.

Depending on the dosage form of the mucosal formulations of the present invention, appropriate method of preparation is employed. Various methods for preparation of mucosal formulations known in the art may be employed.

The compositions of the present invention are useful for the treatment of humans or animals.

In yet another embodiment, the present invention discloses use of fenugreek fiber based excipient for the manufacture of a medicament or formulation that delivers one or more active agent or beneficial agent to the mucosal site of action and/or absorption. In a further embodiment, the present invention discloses use of fenugreek fiber based excipient in formulations for mucosal administration. In another embodiment, the present invention discloses use of fenugreek fiber based excipient in formulations for mucosal administration to provide local or systemic benefits. In one embodiment, the present invention discloses use of fenugreek fiber based excipient in mucosal formulations for treatment or prevention of local or systemic diseases or disorders. In another embodiment, the present invention discloses use of fenugreek fiber based excipient as viscosity modifier in formulations for mucosal administration. In a further embodiment, the present invention discloses use of fenugreek fiber based excipient as bioadhesive agent in formulations for mucosal administration. In yet another embodiment, the present invention discloses use of fenugreek fiber based excipient as gelling agent in formulations for mucosal administration. In a further embodiment, the mucosal

formulations of the present invention comprising fenugreek fiber based excipient provides enhanced bioadhesion or dosage form/formulation retention than otherwise provided by formulations not comprising the excipient. Still another embodiment of the present invention discloses a method of using compositions of the present invention employing fenugreek fiber based excipient comprising administering to a subject in need thereof an effective amount of the composition at the site of mucosal action and/or absorption. In one embodiment the present invention discloses a method of preparing mucosal formulations incorporating fenugreek fiber based excipient in the compositions along with optionally one or more active agents and at least one pharmaceutically acceptable excipient. According to a further aspect of the invention there is provided a method of treatment or prophylaxis of a disease which comprises administration of mucosal formulations of the invention comprising fenugreek fiber based excipient and at least one pharmaceutically acceptable excipient and one or more active agent which is effective against said disease to a patient in need of such treatment.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. The invention is further illustrated by the following examples, which are for illustrative purposes and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Example 1: Nasal gel of cyanocobalamin

Table 1: Composition of cyanocobalamin nasal gel

Ingredients	**%w/w**
Cyanocobalamin, USP	0.5
Fenugreek fiber based excipient	1
Glycerin, USP/NF	10
Propylene glycol, USP/NF	5
Benzalkonium chloride, USP/NF	0.04
Sodium citrate dihydrate, USP/NF	0.5
Citric acid anhydrous, USP/NF	0.2
Sodium hydroxide/hydrochloric acid	q.s. to pH 5.5
Purified water	q.s. to 100

Procedure: The fenugreek fiber based excipient was first dispersed in glycerin and propylene glycol. The other ingredients were dissolved in about 90% of the volume of purified water and filtered. The fenugreek dispersion obtained was then added under vigorous stirring to the filtered solution of other ingredients. The pH was then adjusted and the final weight made.

Example 2: Buccal tablet of fentanyl citrate

Table 2: Composition of fentanyl buccal tablet

Ingredients	**mg/tablet**
Fentanyl citrate equivalent to 0.4mg of fentanyl base	0.628
Fenugreek fiber based excipient	10
Lactose monohydrate, USP/NF	25
Mannitol, USP/NF	35
Microcrystalline cellulose, USP/NF	24.872
Sodium starch glycolate, USP/NF	3
Magnesium stearate, USP/NF	1.5
Total	100

Procedure: All the ingredients except the lubricant were blended. The blend was then lubricated and compressed into tablets.

CLAIMS

We claim:

1. A formulation for mucosal administration comprising fenugreek fiber based excipient and at least one pharmaceutically acceptable excipient.

2. The formulation of claim 1 wherein the fenugreek fiber based excipient comprises fenugreek dietary fibers.

3. The formulation of claim 2 wherein the fenugreek dietary fibers are soluble dietary fibers, insoluble dietary fibers or any combinations thereof.

4. The formulation of claim 3 wherein the fenugreek dietary fibers are a combination of insoluble and soluble dietary fibers.

5. The formulation of claim 4 wherein the insoluble and soluble dietary fibers are present in a ratio of insoluble dietary fibers to soluble dietary fibers of about 0.05 to about 5.

6. The formulation of claim 1 wherein the fenugreek fiber based excipient is substantially free of 4-hydroxyisoleucine, saponins and alkaloids.

7. The formulation of claim 1 wherein the fenugreek fiber based excipient has protein content of not more than about 10% by weight of the fiber based excipient.

8. The formulation of claim 1 wherein the pharmaceutically acceptable excipient is a diluent, a binder, a lubricant, a glidant, a sweetening agent, a flavoring agent, a preservative, a disintegrant, a penetration enhancer, a demulcent, a tonicity adjusting agent, a buffering agent, a pH adjusting agent, a solubilizing agent, a surfactant, a chelating agent, an emulsifying agent, a suspending agent, a

stabilizer, an antioxidant, a release controlling agent, a carrier, a plasticizer, or any combination thereof.

9. The formulation of claim 1 wherein the formulation further comprises viscosity enhancing agent, gelling agent, mucoadhesive agent or any combination thereof.

10. The formulation of claim 1 wherein the formulation is for sublingual, buccal, gingival, palatal, nasal, pulmonary, rectal, or vaginal administration.

11. The formulation of claim 1 wherein the formulation is in the form of a liquid, solid or semisolid dosage form.

12. The formulation of claim 1 wherein the formulation is for providing local or systemic effect.

13. The formulation of claim 1 wherein the formulation further comprises one or more active agents.

14. The formulation of claim 13 wherein the formulation is for immediate release of one or more active agents.

15. The formulation of claim 13 wherein the formulation is for sustained release of one or more active agents.

16. The formulation of claim 1 wherein the formulation is in the form of tablets, pellets, powders, sprays, quick dissolve tablets, lozenges, patches, ointments, gels, gargles, jellies, aerosols, foams, pumps, films, microemulsions, creams, lotions, pastes, solutions, suspensions, suppositories, liposomes, nanoparticles, microparticles, or microspheres.

17. Use of fenugreek fiber based excipient for the manufacture of a medicament for mucosal administration.

18. A method of treatment or prophylaxis of a disease or condition comprising administering to the subject in need thereof a formulation for mucosal

administration comprising one or more active agents effective against said disease or disorder, fenugreek fiber based excipient and at least one pharmaceutically acceptable excipient.