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(54) **Title:** TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ANTI-PROLIFERATE AND ANTI-INFLAMMATORY DRUGS

(57) **Abstract:** Embodiments of the present invention provide a method for treatment of respiratory disorders such as asthma, chronic obstructive pulmonary disease, and chronic sinusitis, including cystic fibrosis, interstitial fibrosis, chronic bronchitis, emphysema, bronchopulmonary dysplasia and neoplasia. The method involves administration, preferably oral, nasal or pulmonary administration, of anti-inflammatory and anti-proliferative drugs (rapamycin or paclitaxel and their analogues) and an additive.

TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ANTI-PROLIFERATE AND ANTI-INFLAMMATORY DRUGS

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application is a continuation-in-part of Application No. 11/942,459, filed November 19, 2007, which claims the benefit of priority of U.S. Provisional Application No. 60/860,084, filed on November 20, 2006, U.S. Provisional Application No. 60/880,742, filed January 17, 2007, U.S. Provisional Application No. 60/897,427, filed on January 25, 2007, U.S. Provisional Application No. 60/903,529 filed on February 26, 2007, U.S. Provisional Application No. 60/904,473 filed March 2, 2007, U.S. Provisional Application No. 60/926,850 filed April 30, 2007, U.S. Provisional Application No. 60/981,380 filed October 19, 2007, and U.S. Provisional Application 60/981,384 filed October 19, 2007, the disclosures of all of which are incorporated by reference herein.

FIELD OF THE INVENTION

[002] Embodiments of the present invention relate to a method for treatment of respiratory disorders such as asthma and chronic obstructive pulmonary disease, including cystic fibrosis, interstitial fibrosis, chronic bronchitis, emphysema, bronchopulmonary dysplasia and neoplasia. The method involves administration, preferably oral, nasal or pulmonary administration, of anti-inflammatory and anti-proliferate drugs (rapamycin or paclitaxel and their analogues).

BACKGROUND OF THE INVENTION

[003] Chronic obstructive pulmonary disease (COPD) is a term used to classify two major airflow obstruction disorders: chronic bronchitis and emphysema. Approximately 16 million Americans have COPD, 80-90% of them were smokers throughout much of their lives. COPD is a leading cause of death in the U.S., accounting for 122,283 deaths in 2003. The cost to the USA for COPD was approximately $20.9 billion in direct health care expenditures in 2003. Chronic bronchitis is inflammation of the bronchial airways. The bronchial airways connect the trachea with the lungs. When inflamed, the bronchial tubes secrete mucus, causing a chronic cough. Emphysema is an overinflation of the alveoli, or air sacs in the lungs. This condition causes shortness of breath.

[004] In emphysema, the alveolar sacs are overinflated as a result of damage to the elastin skeleton of the lung. Inflammatory cells in emphysematous lung release elastase enzymes, which degrade or damage elastin fibers within the lung matrix. Emphysema has a number of causes, including smoking, exposure to environmental pollutants, alpha-one antitrypsin deficiency, and aging.

[005] There are no therapies available today to halt the progression of COPD. Inhaled steroids have recently been studied (Lung Health Study II) as a potential therapy to prevent loss of lung function in emphysema patients. The study concluded, however, that inhaled steroids failed to alter the decline in lung function over time. As patients lose lung function over time, they may become dependent on oxygen, and eventually end up on ventilators to assist with respiration. A relatively new treatment for patients with emphysema is lung volume reduction surgery. Emphysema patients suffer from air trapping in the lungs. This flattens the diaphragm, impairing the ability to inhale and exhale. Patients with emphysema localized to the upper lung lobes are candidates for lung volume reduction surgery, where the upper lobes are surgically removed to restore the natural concavity and function of the diaphragm.

[006] Acute exacerbation of asthma is often caused by spasm of the airways, or bronchoconstriction, causing symptoms including sudden shortness of breath, wheezing, and cough. Bronchospasm is treated with inhaled bronchodilators (anticholinergics such as ipratropium and beta-agonists such as albuterol). Patients inhale these medications into their lungs as a mist, produced by either a nebulizer or a hand-held meter dose (MDI) or dry powder (DPI) inhaler. Patients with acute episodes may also be treated with oral or intravenous steroids that serve to reduce the inflammatory response that exacerbates the condition.

[007] Asthma is a chronic respiratory disease characterized by inflammation of the airways, excess mucus production and airway hyper responsiveness, and a condition in which airways narrow excessively or too easily respond to a stimulus. Asthma episodes or attacks cause narrowing of the airways, which make breathing difficult. Asthma attacks can have a significant impact on a patient's life, limiting participation in many activities. In severe cases, asthma attacks can be life threatening. Presently, there is no known cure for asthma.

[008] According to the American Lung Association, there are approximately 20 million Americans with asthma in 2002. Fourteen million of them were adults. Asthma resulted in approximately 1.9 million emergency room visits in 2002. The estimated direct cost of asthma in the U.S. is $11.5 billion, which is spent on asthma medications, physician office visits, emergency room visits and hospitalizations.

[009] The causes of coronary heart disease and asthma are neointimal proliferation of smooth muscle in arterial vessels and in walls of airways. One aspect of the invention is to deliver paclitaxel or rapamycin and their analogues to the wall of airways to treat the asthma and COPD. Drug coated stents with these drugs have been approved for inhibiting the growth of the smooth muscle cells in vascular arterial vessels.

[010] Chronic sinusitis is an inflammation of the membrane lining of one or more paranasal sinuses. Chronic sinusitis lasts longer than three weeks and often continues for months. In cases of chronic sinusitis, there is usually tissue damage. According to the Center for Disease Control (CDC), thirty seven million cases of chronic sinusitis are reported annually.

[011] Chronic sinusitis is often difficult to treat successfully, however, as some symptoms persist even after prolonged courses of antibiotics. Steroid nasal sprays and prescribed steroids are commonly used to treat inflammation in chronic sinusitis. When medical treatment fails, surgery may be the only alternative in treating chronic sinusitis. Presently, the most common surgery done is functional endoscopic sinus surgery, in which the diseased and thickened tissues from the sinuses are removed to allow drainage. However, there is a need for better medicine for chronic sinusitis.

[012] The present invention provides a new method for treatment of respiratory disorders such as asthma, chronic obstructive pulmonary disease, and chronic sinusitis. The method involves administration, preferably oral, nasal or pulmonary administration, of anti-inflammatory and anti-proliferate drugs (rapamycin or paclitaxel and their analogues) and an additive. Embodiments of the present invention provide a pharmaceutical formulation comprising a drug for treatment of the respiratory system, and an additive that enhances absorption of the drug into tissue of body passages.

SUMMARY OF THE INVENTION

[013] Embodiments of the present invention are directed to the treatment of respiratory disorders by intratracheal administration of an effective amount of anti-inflammatory and anti-proliferate drugs (rapamycin or paclitaxel and their analogues). Respiratory disorders such as asthma, chronic obstructive pulmonary disease, and chronic sinusitis include cystic fibrosis, interstitial fibrosis, chronic bronchitis, emphysema, nasal and sinus dysplasia, bronchopulmonary dysplasia and neoplasia. The treatment is intended for a variety of animals, such as premature neonates to adult humans. Administration of rapamycin or paclitaxel may be performed by aerosol, which can be generated by a nebulizer, by inhalation or by instillation. The rapamycin or paclitaxel may be administered alone or with an additive carrier in solution such as saline solution, DMSO, alcohol, or water. It may also be used as combinations with inhaled bronchodilators (anticholinergics such as ipratropium and beta-agonists such as albuterol) and oral or intravenous steroids. Patients inhale these medications into their lungs as a mist, produced by either a nebulizer or a hand-held meter dose (MDI) or dry powder (DPI) inhaler.

[014] The additive has a hydrophilic part and a drug affinity part. The drug affinity part is a hydrophobic part and/or has an affinity to the therapeutic agent by hydrogen bonding and/or van der Waals interactions. The drug affinity part may include aliphatic and aromatic organic hydrocarbon compounds, such as benzene, toluene, and alkanes, among others. These parts are not water soluble. They have no covalently bonded iodine. The hydrophilic part may include hydroxyl groups, amine groups, amide groups, carbonyl groups, carboxylic acid and anhydrides, ethyl oxide, ethyl glycol, polyethylene glycol, ascorbic acid, amino acid, amino alcohol, glucose, sucrose, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic salts and their substituted molecules, among others. These parts can dissolve in water and polar solvents. These additives are not oils, lipids, or polymers. The therapeutic agent is not enclosed in micelles or liposomes or encapsulated in polymer particles.

[015] Embodiments of the present invention provide a method for treating the lung during an acute episode of reversible chronic obstructive pulmonary disease. The coronary and peripheral diseases result from smooth muscle cell proliferation. Asthma includes episodes or attacks of the airway narrowing,

contracting and thickening via smooth muscle cell proliferation. The rapamycin, paclitaxel, and their analogues can be used for treating asthma in the lung.

[016] Embodiments of the present invention provide a method of treating respiratory disorders such as asthma, chronic obstructive pulmonary disease and chronic sinusitis in a mammal comprises administrating an antiproliferative and anti-inflammatory effective amount of rapamycin, or paclitaxel or their analogues to said mammal orally, parenterally, intravascularly, intranasally, intrabronchially, transdermally, rectally, or via an impregnated vascular stent or balloon catheter.

[017] In one embodiment, the present invention relates to a method for treating a respiratory disorder, such as at least one of asthma, chronic obstructive pulmonary disease, and chronic sinusitis, in a mammal comprising administering a pharmaceutical formulation comprising an effective amount of a drug and an additive to said mammal orally, parenterally, intravascularly, intranasally, intrabronchially, transdermally, rectally, or via an impregnated vascular stent or balloon catheter into a body passage, wherein said drug is chosen from rapamycin and analogues thereof and paclitaxel and analogues thereof. In one aspect of this embodiment, the respiratory disorder, such as asthma and chronic obstructive pulmonary disease, is chosen from chronic bronchitis, cystic fibrosis, interstitial fibrosis, nasal and sinus dysplasia, bronchopulmonary dysplasia and neoplasia, and emphysema. In another aspect of this embodiment, the administering comprises delivery via a mist route chosen from aerosol inhalation, dry powder inhalation, liquid inhalation, and liquid instillation. In one embodiment, the mist is produced by either a nebulizer, a hand-held meter dose inhaler (MDI), or dry powder (DPI) inhaler.

[018] In one embodiment of the method, the additive enhances absorption of the drug into tissue of the body passage of the respiratory and sinus system. In another embodiment of the method, the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions. In another embodiment, the drug is not enclosed in micelles or encapsulated in polymer particles. In yet another embodiment, the pharmaceutical formulation does not include oil, a lipid, or a polymer.

[019] In one embodiment of the method, the additive is at least one of a surfactant and a chemical compound. In one embodiment, the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In one embodiment, the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof. In another embodiment, the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups. In another embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

[020] In another embodiment, the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside,

nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

[021] In one embodiment, the surfactant is chosen from PEG-fatty acids and PEG-fatty acid mono and diesters, polyethylene glycol glycerol fatty acid

esters, alcohol-oil transesterification products, polyglyceryl fatty acids, propylene glycol fatty acid esters, sterols and derivatives thereof, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, and sorbitan fatty acid esters. In another embodiment, the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil, PEG-8 caprylic /capric glycerides, and PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium

chloride, cetylpyridinium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, edrophonium chloride, domiphen bromide, dialkylesters of sodium sulfonsuccinic acid, sodium dioctyl sulfosuccinate, sodium cholate, sodium taurocholate, and derivatives thereof.

[022] In one embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine (Aminoacids); acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid (organic acids and anhydrides); cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U (vitamins); albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine,

benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols, and derivatives thereof.

[023] In one embodiment of the method, the pharmaceutical formulation further comprises an additional drug. In one aspect of this embodiment, the additional drug is chosen from corticosteroids, anticholinergics, beta-agonists, non-steroidal anti-inflammatory drugs, macrolide antibiotics, bronchodilators, leukotriene receptor inhibitors, cromolyn sulfate, and combinations thereof.

[024] In one embodiment, the additive is chosen from PEG fatty esters and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, vitamins and derivatives, aminoacids, multiaminoacids and derivatives, peptides, polypeptides, proteins, quaternary ammonium salts, organic acids, salts and anhydrides. In another embodiment, the additive in the coating layer overlying the surface of the balloon is chosen from p-isononylphenoxypolyglycidol, PEG laurate, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid (ionic surfactants), cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine (amino acids); acetic anhydride, benzoic anhydride, ascorbic

acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid (organic acids and anhydrides); cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U (vitamins); albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, triethanolamine, diethanolamine, meglumine, tromethamine, glucamine, glucosamine, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, vanillin, vanillic acid, vanillic acid diethylamide, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, acetaminophen, ibuprofen, catechin, catechin gallate, methyl paraben, ethyl paraben, propyl paraben, butyl paraben, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine above described, polyglycidol, glycerols and multiglycerols (chemical compounds with multiple hydroxyl, amino, carbonyl, carboxyl, or ester moieties).

[025] In another aspect of this embodiment, the ionic surfactant is chosen from benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, edrophonium chloride, domiphen bromide, and dialkylesters of sodium sulfonsuccinic acid, sodium dioctyl sulfosuccinate, sodium cholate, and sodium taurocholate.

[026] In one embodiment of the method, the additive is chosen from PEG-fatty acids and PEG-fatty acid mono and diesters, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglyceryl fatty acids, propylene glycol fatty acid esters, sterols and derivatives thereof, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugars and

derivatives thereof, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, fat-soluble vitamins and salts thereof, water-soluble vitamins and amphiphilic derivatives thereof, amino acid and salts thereof, oligopeptides, peptides and proteins, and organic acids and esters and anhydrides thereof.

[027] In another embodiment of the method, the additive is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, and PEG-20 oleate. In another embodiment, the additive is chosen from PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate and PEG-32 dioleate. In another embodiment of the method, the additive is chosen from PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, and PEG-30 glyceryl oleate. In another embodiment of the method, the additive is chosen from PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil, PEG-8 caprylic /capric glycerides, and PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, and PEG-20 almond glycerides.

[028] In another embodiment of the method, the additive is chosen from polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate. In another embodiment of the method, the additive is chosen from propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, and propylene glycol dioctanoate. In another embodiment of the method, the additive is PEG-24 cholesterol ether. In another embodiment of the method, the additive is chosen from sterol polyethylene glycol derivatives.

[029] In another embodiment of the method, the additive is chosen from PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, and PEG-20 sorbitan monooleate. In another embodiment of the method, the additive is chosen from PEG-3 oleyl ether and PEG-4 lauryl ether. In another embodiment of the method, the additive is chosen from sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, and octyl - β -D-thioglucopyranoside.

[030] In another embodiment of the method, the additive is chosen from PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, and nonoxynol. In another embodiment of the method, the additive is chosen from poloxamer 108, poloxamer 188, poloxamer 217, poloxamer 238, poloxamer 288, poloxamer 338, and poloxamer 407. In another embodiment of the method, the additive is chosen from poloxamer 124, poloxamer 182, poloxamer 183, poloxamer 212, poloxamer 331, and poloxamer 335. In another embodiment of the method, the additive is chosen from sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, and sorbitan monostearate. In another embodiment of the method, the additive is chosen from alpha-tocopherol, beta-tocopherol, gamma-tocopherol, delta-tocopherol, tocopherol acetate, ergosterol, 1-alpha-hydroxycholecal- ciferol, vitamin D2, vitamin D3, alpha-carotene, beta-carotene, gamma-carotene, vitamin A, fursultiamine, methylolriboflavin, octotiamine, prosultiamine, riboflavine, vintiamol, dihydrovitamin K1, menadiol diacetate, menadiol dibutyrate, menadiol disulfate, menadiol, vitamin K1, vitamin K1 oxide, vitamins K2, and vitamin K-S(II), and folic acid.

[031] In another embodiment of the method, the additive is chosen from acetiamine, benfotiamine, pantothenic acid, cetotiamine, cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U. In another embodiment of the method, the

additive is chosen from alanine, arginine, asparagines, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, proline, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine, and salts of any of the foregoing. In another embodiment of the method, the additive is albumin. In another embodiment of the method, the additive is chosen from n-octyl-β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, L-ascorbic acid, thiamine, maleic anhydride, niacinamide, and 2-pyrrolidone-5-carboxylic acid.

[032] In another embodiment of the method, the additive is chosen from riboflavin, riboflavin-phosphate sodium, Vitamin D3, folic acid, vitamin 12, diethylenetriaminepentaacetic acid dianhydride, ethylenediaminetetraacetic dianhydride, maleic acid and anhydride, succinic acid and anhydride, diglycolic anhydride, glutaric anhydride, L-ascorbic acid, thiamine, nicotinamide, nicotinic acid, 2-pyrrolidone-5-carboxylic acid, cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine.

[033] In another embodiment of the method, the additive is chosen from isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, and polyglyceryl-10 stearate. In another embodiment of the method, the additive is chosen from L-ascorbic acid, thiamine, maleic acids, niacinamide, and 2-pyrrolidone-5-carboxylic acid. In another embodiment of the method, the additive is chosen from Vitamin D2 and D3.

[034] In one embodiment, the present invention relates to a pharmaceutical formulation comprising an effective amount of a drug for treatment of a respiratory or sinus system, and an additive that enhances absorption of the drug into tissue of the respiratory system. In one aspect of this embodiment, the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by

hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions. In another aspect of this embodiment, the drug is not enclosed in micelles or encapsulated in polymer particles. In another aspect of this embodiment, the formulation does not include oil, a lipid, or a polymer. In yet another aspect of this embodiment, the formulation is an aqueous aerosol formulation, a dry powder aerosol formulation, or a propellant-based formulation.

[035] In one embodiment of the pharmaceutical formulation, the drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof. In one aspect of this embodiment, the drug is present in a concentration of about 0.05 mg/ml to about 600 mg/ml.

[036] In one embodiment of the pharmaceutical formulation, the additive is at least one of a surfactant and a chemical compound. In one embodiment, the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In one embodiment, the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof. In one embodiment, the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups. In one aspect of this embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In another aspect of this embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic

anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid ; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine above described, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, and acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols and a mixture of the additives, and their derivatives.

[037] In one embodiment of the pharmaceutical formulation, the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate,

plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid,

salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

[038] In one embodiment of the pharmaceutical formulation, the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate,, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil,, PEG-8 caprylic /capric glycerides, PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-3 oleyl ether and PEG-4 lauryl ether, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop-

yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid (ionic surfactants), n-octyl- β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, and their derivatives.

[039] In one embodiment of the pharmaceutical formulation, the additive is chosen from from PEG-fatty acids and PEG-fatty acid mono and diesters, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglyceryl fatty acids, propylene glycol fatty acid esters, sterol and derivatives thereof, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugars and derivatives thereof, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, fat-soluble vitamins and salts thereof, water-soluble vitamins and amphiphilic derivatives thereof, amino acid and salts thereof, oligopeptides, peptides and proteins, and organic acids and esters and anhydrides thereof. In another embodiment of the pharmaceutical formulation, the additive is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, and PEG-20 oleate.

[040] In one embodiment of the pharmaceutical formulation, the additive is chosen from PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate and PEG-32 dioleate. In another embodiment of the pharmaceutical formulation, the additive is chosen from PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, and PEG-30 glyceryl oleate. In another embodiment of the pharmaceutical formulation, the additive is

chosen from PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil, PEG-8 caprylic /capric glycerides, PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, and PEG-20 almond glycerides.

[041] In one embodiment of the pharmaceutical formulation, the additive is chosen from polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate. In another embodiment of the pharmaceutical formulation, the additive is chosen from propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, and propylene glycol dioctanoate.

[042] In one embodiment of the pharmaceutical formulation, the additive is PEG-24 cholesterol ether. In another embodiment of the pharmaceutical formulation, the additive is chosen from sterol polyethylene glycol derivatives. In another embodiment of the pharmaceutical formulation, the additive is chosen from PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, and PEG-20 sorbitan monooleate. In another embodiment of the pharmaceutical formulation, the additive is chosen from PEG-3 oleyl ether and PEG-4 lauryl ether.

[043] In one embodiment of the pharmaceutical formulation, the additive is chosen from sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, and

octyl - β -D-thioglucopyranoside. In another embodiment of the pharmaceutical formulation, the additive is chosen from PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, and nonoxynol. In another embodiment of the pharmaceutical formulation, the additive is chosen from poloxamer 108, poloxamer 188, poloxamer 217, poloxamer 238, poloxamer 288, poloxamer 338, and poloxamer 407. In another embodiment of the pharmaceutical formulation, the additive is chosen from poloxamer 124, poloxamer 182, poloxamer 183, poloxamer 212, poloxamer 331, and poloxamer 335.

[044] In one embodiment of the pharmaceutical formulation, the additive is chosen from sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, and sorbitan monostearate. In another embodiment of the pharmaceutical formulation, the additive is chosen from alpha-tocopherol, beta-tocopherol, gamma-tocopherol, delta-tocopherol, tocopherol acetate, ergosterol, 1-alpha-hydroxycholecal- ciferol, vitamin D2, vitamin D3, alpha-carotene, beta-carotene, gamma-carotene, vitamin A, fursultiamine, methylolriboflavin, octotiamine, prosultiamine, riboflavine, vintiamol, dihydrovitamin K1, menadiol diacetate, menadiol dibutyrate, menadiol disulfate, menadiol, vitamin K1, vitamin K1 oxide, vitamins K2, and vitamin K--S(II), and folic acid.

[045] In another embodiment of the pharmaceutical formulation, the additive is chosen from acetiamine, benfotiamine, pantothenic acid, cetotiamine, cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U. In another embodiment of the pharmaceutical formulation, the additive is chosen from alanine, arginine, asparagines, aspartic acid, cysteine, cystine, glutamic acid, glutamine, glycine, histidine, proline, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine, and salts of any of the foregoing. In another embodiment of the pharmaceutical formulation, the additive is albumin.

[046] In one embodiment of the pharmaceutical formulation, the additive is chosen from n-octyl- β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan

monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, L-ascorbic acid, thiamine, maleic anhydride, niacinamide, and 2-pyrrolidone-5-carboxylic acid. In another embodiment of the pharmaceutical formulation, the additive is chosen from riboflavin, riboflavin-phosphate sodium, Vitamin D3, folic acid, vitamin 12, diethylenetriaminepentaacetic acid dianhydride, ethylenediaminetetraacetic dianhydride, maleic acid and anhydride, succinic acid and anhydride, diglycolic anhydride, glutaric anhydride, L-ascorbic acid, thiamine, nicotinamide, nicotinic acid, 2-pyrrolidone-5-carboxylic acid, cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine.

[047] In one embodiment of the pharmaceutical formulation, the additive is chosen from isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, and polyglyceryl-10 stearate. In another embodiment of the pharmaceutical formulation, the additive is chosen from L-ascorbic acid, thiamine, maleic acids, niacinamide, and 2-pyrrolidone-5-carboxylic acid. In another embodiment of the pharmaceutical formulation, the additive is chosen from Vitamin D2 and D3.

[048] In one embodiment of the pharmaceutical formulation, the drug is present in a concentration of about 0.05 mg/g to about 990 mg/g. In another embodiment of the pharmaceutical formulation, the formulation further comprises an additional drug. In one aspect of this embodiment, the additional drug is chosen from corticosteroids, anticholinergics, beta-agonists, non-steroidal anti-inflammatory drugs, macrolide antibiotics, bronchodilators, leukotriene receptor inhibitors, cromolyn sulfate, and combinations thereof.

[049] In one embodiment, the present invention relates to a method for treating a respiratory system in a mammal comprising (1) forming an aerosol of a dispersion of particles, wherein the particles comprise a water insoluble drug and an additive that enhances absorption of the drug into tissue of the respiratory system, and (2) administering the aerosol to the respiratory system of the mammal. In one aspect of this embodiment, the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part

that has an affinity to the therapeutic agent by van der Waals interactions. In another aspect of this embodiment, the drug is not enclosed in micelles or encapsulated in polymer particles. In another aspect of this embodiment, the dispersion does not include oil, a lipid, or a polymer. In another aspect of this embodiment, the dispersion does not include a purely hydrophobic additive.

[050] In one embodiment, the additive is at least one of a surfactant and a chemical compound. In one embodiment, the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In one embodiment, the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof. In one embodiment, the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups. In one aspect of this embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In another aspect of this embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid ; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic

acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine above described, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols and a mixture of the additives, and their derivatives.

[051] In one embodiment, the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside,

n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

[052] In one embodiment, the additive is chosen from PEG-fatty acids and PEG-fatty acid mono and diesters, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglyceryl fatty acids, propylene glycol fatty acid esters, sterol and derivatives thereof, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugars and derivatives thereof, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, fat-soluble vitamins and salts thereof, water-soluble vitamins and amphiphilic derivatives thereof, amino acid and salts thereof, oligopeptides, peptides and proteins, and organic acids and esters and anhydrides thereof. In yet another aspect of this embodiment, the water insoluble drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof.

[053] In one embodiment, the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil, PEG-8 caprylic /capric glycerides, PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan

monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-3 oleyl ether and PEG-4 lauryl ether, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid (ionic surfactants), n-octyl- β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, and their derivatives.

[054] In one embodiment, the water insoluble drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof.

[055] In one embodiment, the present invention relates to an aerosol device for delivering a drug to a respiratory system, the device comprising a pharmaceutical formulation comprising a water insoluble drug and an additive, wherein the additive enhances absorption of the drug into tissue of the respiratory system. In one aspect of this embodiment, the pharmaceutical formulation is an aqueous, propellant based, or dry powder formulation. In another aspect of this embodiment, the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions. In another aspect of this embodiment, the drug is not enclosed in micelles or encapsulated in polymer particles. In another aspect of this embodiment, the formulation does not include oil, a lipid, or a polymer. In another aspect of this embodiment, the additive is

chosen from PEG-fatty acids and PEG-fatty acid mono and diesters, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglyceryl fatty acids, propylene glycol fatty acid esters, sterol and derivatives thereof, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugars and derivatives thereof, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, fat-soluble vitamins and salts thereof, water-soluble vitamins and amphiphilic derivatives thereof, amino acid and salts thereof, oligopeptides, peptides and proteins, and organic acids and esters and anhydrides thereof. In another aspect of this embodiment, the water insoluble drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof. In yet another aspect of this embodiment, the aerosol device is one of a nebulizer, a hand-held meter dose inhaler, or a dry powder inhaler.

[056] In another embodiment, the additive is at least one of a surfactant and a chemical compound. In one embodiment, the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In one embodiment, the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof.

[057] In one embodiment, the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups. In one aspect of this embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In another aspect of this embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid,

amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid ; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine above described, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols and a mixture of the additives, and their derivatives.

[058] In one embodiment, the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl

stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-

cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

[059] In one embodiment, the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate,, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil,, PEG-8 caprylic /capric glycerides, PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-3 oleyl ether and PEG-4 lauryl ether, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-

maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid (ionic surfactants), n-octyl- β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, and their derivatives.

[060] In one embodiment, the water insoluble drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof. In one embodiment, the aerosol device is one of a nebulizer, a hand-held meter dose inhaler, or a dry powder inhaler.

[061] In one embodiment, the present invention relates to a device sized and configured for insertion into a passage of a respiratory system, the device comprising a layer overlying an exterior surface of the device, the layer comprising a water insoluble drug for the treatment of the respiratory system and an additive that enhances absorption of the drug into tissue of the respiratory system. In one aspect of this embodiment, the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions. In another aspect of this embodiment, the drug is not enclosed in micelles or encapsulated in polymer particles. In another aspect of this embodiment, the layer does not include oil, a lipid, or a polymer. In another aspect of this embodiment, the layer does not include a purely hydrophobic additive. In another aspect of this embodiment, the device is a balloon catheter or a stent. In another aspect of this embodiment, the water insoluble drug is chosen from paclitaxel and analogues

thereof and rapamycin and analogues thereof. In another apsect of this embodiment, the additive is chosen from PEG-fatty acids and PEG-fatty acid mono and diesters, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglyceryl fatty acids, propylene glycol fatty acid esters, sterol and derivatives thereof, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugars and derivatives thereof, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, fat-soluble vitamins and salts thereof, water-soluble vitamins and amphiphilic derivatives thereof, amino acid and salts thereof, oligopeptides, peptides and proteins, and organic acids and esters and anhydrides thereof.

[062] In one embodiment, the additive is at least one of a surfactant and a chemical compound. In one embodiment, the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In one embodiment, the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof.

[063] In one embodiment, the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups. In one aspect of this embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In another aspect of this embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine;

acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid ; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine above described, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols and a mixture of the additives, and their derivatives.

[064] In one embodiment, the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-

10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols,

galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

[065] In one embodiment, the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil, PEG-8 caprylic /capric glycerides, PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-3 oleyl ether and PEG-4 lauryl ether, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-

glucopyranoside, octyl - β -D-thioglucopyranoside, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid (ionic surfactants), n-octyl- β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, and their derivatives.

[066] In one embodiment, the present invention relates to a method for treating a respiratory system comprising inserting a balloon catheter comprising a coating layer into an airway, wherein the coating layer comprises a drug and an additive, inflating the balloon catheter and releasing the drug to a wall of the airway, deflating the balloon; and withdrawing the balloon catheter from the airway. In one aspect of this embodiment, the additive enhances absorption of the drug into tissue of the respiratory or sinus system. In another aspect of this embodiment, the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions. In another aspect of this embodiment, the drug is not enclosed in micelles or encapsulated in polymer particles. In another aspect of this embodiment, the coating layer does not include oil, a lipid, or a polymer. In another aspect of this embodiment, the coating layer does not include a purely hydrophobic additive. In another aspect of this embodiment, the drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof. In another aspect of this embodiment, the additive is chosen from PEG-fatty acids and PEG-fatty acid mono and diesters, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglyceryl fatty acids, propylene glycol fatty acid esters, sterol and derivatives thereof, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugars and derivatives thereof, polyethylene glycol alkyl phenols,

polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, fat-soluble vitamins and salts thereof, water-soluble vitamins and amphiphilic derivatives thereof, amino acid and salts thereof, oligopeptides, peptides and proteins, and organic acids and esters and anhydrides thereof. In yet another aspect of this embodiment, the drug can be released to the wall of the airway prior to, during, or after an asthma attack.

[067] In one embodiment, the additive is at least one of a surfactant and a chemical compound. In one embodiment, the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules. In one embodiment, the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof.

[068] In one embodiment, the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups. In one aspect of this embodiment, the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

[069] In one embodiment, the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan

monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol),

penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

[070] It is understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the present invention as claimed.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[071] Embodiments of the present invention provide a method for treatment of respiratory disorders such as asthma, chronic obstructive pulmonary disease and chronic sinusitis, including cystic fibrosis, interstitial fibrosis, chronic bronchitis, emphysema, nasal and sinus dysplasia, bronchopulmonary dysplasia and neoplasia. According to embodiments, the method involves administration, preferably oral or pulmonary administration, of anti-inflammatory and anti-proliferate drugs (rapamycin or paclitaxel and their analogues). The anti-inflammatory and anti-proliferate drugs can be administered alone or with one or more additives.

[072] The anti-inflammatory and anti-proliferate drugs intended for intranasal delivery (systemic and local) for treatment of respiratory disorders such as asthma, COPD and chronic sinusitis can be, administered as aqueous solutions or suspensions, as solutions or suspensions in halogenated hydrocarbon propellants (pressurized metered-dose inhalers), or as dry powders. Metered-dose spray pumps for aqueous formulations, pMDIs, and DPIs for nasal delivery, are available from, for example, Valois of America or Pfeiffer of America.

[073] The drugs intended for pulmonary delivery can also be administered as aqueous formulations, as suspensions or solutions in halogenated hydrocarbon propellants, or as dry powders. Aqueous formulations must be aerosolized by liquid nebulizers employing either hydraulic or ultrasonic atomization, propellant-based systems require suitable pressurized metered-dose inhalers (pMDIs), and dry powders require dry powder inhaler devices (DPIs), which are capable of dispersing the drug substance effectively. For aqueous and other non-pressurized liquid systems, a variety of nebulizers (including small volume nebulizers) are available to aerosolize the formulations. Compressor-driven nebulizers incorporate jet technology and use compressed air to generate the liquid aerosol. Such devices

are commercially available from, for example, Healthdyne Technologies, Inc.; Invacare, Inc.; Mountain Medical Equipment, Inc.; Pari Respiratory, Inc.; Mada Medical, Inc.; Puritan-Bennet; Schuco, Inc., DeVilbiss Health Care, Inc.; and Hospitak, Inc. Ultrasonic nebulizers rely on mechanical energy in the form of vibration of a piezoelectric crystal to generate respirable liquid droplets and are commercially available from, for example, Omron Heathcare, Inc. and DeVilbiss Health Care, Inc.

[074] A propellant driven inhaler (pMDI) releases a metered dose of medicine upon each actuation. The medicine is formulated as a suspension or solution of a drug substance in a suitable propellant such as a halogenated hydrocarbon. pMDIs are described in, for example, Newman, S. P., Aerosols and the Lung, Clarke et al., eds., pp. 197-224 (Butterworths, London, England, 1984).

[075] Dry powder inhalers (DPIs), which involve disaggregation and aerosolization of dry powders, normally rely upon a burst of inspired air that is drawn through the unit to deliver a drug dosage. Such devices are described in, for example, U.S. Pat. No. 4,807,814, which is directed to a pneumatic powder ejector having a suction stage and an injection stage; SU 628930 (Abstract), describing a hand-held powder disperser having an axial air flow tube; Fox et al., Powder and Bulk Engineering, pages 33-36 (March 1988), describing a venturi eductor having an axial air inlet tube upstream of a venturi restriction; EP 347 779, describing a hand-held powder disperser having a collapsible expansion chamber; and U.S. Pat. No. 5,785,049 directed to dry powder delivery devices for drugs.

[076] Droplet/particle size determines deposition site. In developing the therapeutic aerosol of the anti-inflammatory and anti-proliferate drugs, the aerodynamic size distribution of the inhaled particles is the single most important variable in defining the site of droplet or particle deposition in the patient; in short, it will determine whether drug targeting succeeds or fails. See P. Byron, "Aerosol Formulation, Generation, and Delivery Using Nonmetered Systems," Respiratory Drug Delivery, 144-151, 144 (CRC Press, 1989). Thus, a prerequisite in developing a therapeutic aerosol is a preferential particle size. The deposition of inhaled aerosols involves different mechanisms for different size particles. D. Swift (1980); Parodi et al., "Airborne Particles and Their Pulmonary Deposition," in Scientific Foundations of Respiratory Medicine, Scaddings et al. (eds.), pp. 545-557 (W. B.

Saunders, Philadelphia, 1981); J. Heyder, "Mechanism of Aerosol Particle Deposition," Chest, 80:820-823 (1981).

[077] Generally, inhaled particles are subject to deposition by one of two mechanisms: impaction, which usually predominates for larger particles, and sedimentation, which is prevalent for smaller particles. Impaction occurs when the momentum of an inhaled particle is large enough that the particle does not follow the air stream and encounters a physiological surface. In contrast, sedimentation occurs primarily in the deep lung when very small particles which have traveled with the inhaled air stream encounter physiological surfaces as a result of random diffusion within the air stream. For intranasally administered drug compounds which are inhaled through the nose, it is desirable for the drug to impact directly on the nasal mucosa; thus, large (ca. 5 to 100 microns) particles or droplets are generally preferred for targeting of nasal delivery.

[078] Pulmonary drug delivery of the anti-inflammatory and anti-proliferative drugs is accomplished by inhalation of an aerosol through the mouth and throat. Particles having aerodynamic diameters of greater than about 5 microns generally do not reach the lung; instead, they tend to impact the back of the throat and are swallowed and possibly orally absorbed. Particles having diameters of about 2 to about 5 microns are small enough to reach the upper- to mid-pulmonary region (conducting airways), but are too large to reach the alveoli. Even smaller particles, i. e., about 0.5 to about 2 microns, are capable of reaching the alveolar region. Particles having diameters smaller than about 0.5 microns can also be deposited in the alveolar region by sedimentation, although very small particles may be exhaled.

[079] Embodiments of the present invention are directed to aqueous, propellant-based, and dry powder aerosols of anti-inflammatory and anti-proliferate drug compositions, for pulmonary delivery, in which essentially every inhaled particle contains at least one anti-inflammatory and anti-proliferate drug particle. The drug is highly water-insoluble. Preferably, the anti-inflammatory and anti-proliferate drug has an effective average particle size of about 5 micron or less.

A. Aqueous Aerosol Formulations

[080] Embodiments of the present invention encompass aqueous formulations comprising drug particles and an additive. For aqueous aerosol

formulations, the anti-inflammatory and anti-proliferate drug may be present at a concentration of about 0.05 mg/ml up to about 600 mg/ML. Such formulations provide effective delivery to appropriate areas of the lung. In addition, the more concentrated aerosol formulations (i.e., for aqueous aerosol formulations, about 10 mg/ml up to about 600 mg/ml) have the additional advantage of enabling large quantities of drug substance to be delivered to the lung in a very short period of time.

B. Dry Powder Aerosol Formulations

[081] Another embodiment of the invention is directed to dry powder aerosol formulations comprising anti-inflammatory and anti-proliferate drug particles and an additive for pulmonary and nasal administration. Dry powders, which can be used in both DPIs and pMDIs, can be made by spray drying aqueous drug dispersions. Alternatively, dry powders containing anti-inflammatory and anti-proliferate drug can be made by freeze-drying drug dispersions. Combinations of spray-dried and freeze-dried drug powders can be used in DPIs and pMDIs. For dry powder aerosol formulations, the anti-inflammatory and anti-proliferate drug may be present at a concentration of about 0.05 mg/g up to about 990 mg/g.

1.Spray-Dried Powders Containing Anti-inflammatory and Anti-proliferate Drug

[082] Powders comprising anti-inflammatory and anti-proliferate drug can be made by spray-drying aqueous dispersions of a drug and an additive to form a dry powder which consists of aggregated drug particles having an additive. The aggregates can have a size of about 1 to about 2 microns, which is suitable for deep lung delivery. The aggregate particle size can be increased to target alternative delivery sites, such as the upper bronchial region or nasal mucosa by increasing the concentration of drug in the spray-dried dispersion or by increasing the droplet size generated by the spray dryer.

[083] Alternatively, the aqueous dispersion of the anti-inflammatory and anti-proliferate drug and additive can contain a dissolved diluent such as lactose or mannitol which, when spray dried, forms respirable diluent particles, each of which contains at least one embedded drug particle and additive. The diluent particles with embedded drug can have a particle size of about 1 to about 2 microns, suitable for deep lung delivery. In addition, the diluent particle size can be

increased to target alternate delivery sites, such as the upper bronchial region or nasal mucosa by increasing the concentration of dissolved diluent in the aqueous dispersion prior to spray drying, or by increasing the droplet size generated by the spray dryer.

[084] Spray-dried powders can be used in DPIs or pMDIs, either alone or combined with freeze-dried particulate powder. In addition, spray-dried powders containing drug particles can be reconstituted and used in either jet or ultrasonic nebulizers to generate aqueous dispersions having respirable droplet sizes, where each droplet contains at least one drug particle. Concentrated particulate dispersions may also be used in these aspects of the invention.

2. Freeze-Dried Powders Containing Anti-inflammatory and Anti-proliferative Particulate Drug

[085] The particulate drug dispersions can also be freeze-dried to obtain powders suitable for nasal or pulmonary delivery. Such powders may contain aggregated particulate drug particles having an additive. Such aggregates may have sizes within a respirable range, i.e., about 2 to about 5 microns.

[086] Freeze dried powders of the appropriate particle size can also be obtained by freeze drying aqueous dispersions of the anti-inflammatory and anti-proliferative drug and additive, which additionally contain a dissolved diluent such as lactose or mannitol. In these instances the freeze dried powders consist of respirable particles of diluent, each of which contains at least one embedded drug particle.

[087] Freeze-dried powders can be used in DPIs or pMDIs, either alone or combined with spray-dried particulate powder. In addition, freeze-dried powders containing drug particles can be reconstituted and used in either jet or ultrasonic nebulizers to generate aqueous dispersions having respirable droplet sizes, where each droplet contains at least one drug particle. Concentrated particulate dispersions may also be used in these aspects of the invention.

C. Propellant-Based Formulations

[088] Yet another embodiment of the invention is directed to a process and composition for propellant-based systems comprising anti-inflammatory and anti-proliferative drug particles and an additive. Such formulations may be prepared by wet milling the coarse drug substance and additive in liquid propellant, either at

ambient pressure or under high pressure conditions. Alternatively, dry powders containing drug particles may be prepared by spray-drying or freeze-drying aqueous dispersions of drug particles and additive; the resultant powders are dispersed into suitable propellants for use in conventional pMDIs. Such particulate pMDI formulations can be used for either nasal or pulmonary delivery. For pulmonary administration, such formulations afford increased delivery to the deep lung regions because of the small (i.e., about 1 to about 2 microns) particle sizes available from these methods. Concentrated aerosol formulations can also be employed in pMDIs.

D. Methods of Making Aerosol Formulations

[089] In embodiments, the invention also provides methods for making an aerosol comprising a drug particulate composition comprising an anti-inflammatory and anti-proliferate and an additive. The particulate dispersions used in making aqueous aerosol compositions can be made by wet milling or by precipitation methods known in the art. Dry powders containing the drug particles and additive can be made by spray-drying or freeze-drying aqueous dispersions of the anti-inflammatory and anti-proliferate drug particles and the additive. The dispersions used in these systems may or may not contain dissolved diluent material prior to drying. Additionally, both pressurized and non-pressurized milling operations can be employed to make particulate drug compositions in non-aqueous systems.

[090] In a non-aqueous, non-pressurized milling system, a non-aqueous liquid which has a vapor pressure of 1 atm or less at room temperature is used as a milling medium and may be evaporated to yield dry particulate drug and additive. The non-aqueous liquid may be, for example, a high-boiling halogenated hydrocarbon. The dry particulate drug composition thus produced may then be mixed with a suitable propellant or propellants and used in a conventional pMDI.

[091] Alternatively, in a pressurized milling operation, a non-aqueous liquid which has a vapor pressure >1 atm at room temperature is used as a milling medium for making a particulate drug and additive composition. Such a liquid may be, for example, a halogenated hydrocarbon propellant which has a low boiling point. The resultant particulate composition can then be used in a conventional pMDI without further modification, or can be blended with other suitable propellants. Concentrated aerosols may also be made via such methods.

E. Methods of Using particulate Aerosol Formulations

[092] In yet another aspect of the invention, there is provided a method of treating asthma and COPD of mammals comprising: (1) forming an aerosol of a dispersion (either aqueous or powder) of the anti-inflammatory and anti-proliferate drug particles, wherein the particles comprise an insoluble drug having an additive on the surface thereof, and (2) administering the aerosol to the pulmonary or nasal cavities of the mammal. Concentrated aerosol formulations may also be used in such methods.

Drugs and Drug Combinations

[093] The therapeutic drug or agent in the invention comprises one or more drugs or agents chosen from an anti-thrombosis agent, an anti-proliferate agent, an anti-inflammatory agent, an anti-coagulant, an agent affecting extra cellular matrix production and organization, and a vasodilating agent.

[094] Examples of the therapeutic agents or drugs that are suitable for use in accordance with the present invention include sirolimus, everolimus, actinomycin D (ActD), taxol, paclitaxel, or derivatives and analogs thereof. Examples of agents include other antiproliferative substances as well as antineoplastic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, and antioxidant substances. Examples of antineoplastics include taxol (paclitaxel and docetaxel). Further examples of therapeutic drugs or agents include antiplatelets, anticoagulants, antifibrins, antiinflammatories, antithrombins, and antiproliferatives. Examples of antiplatelets, anticoagulants, antifibrins, and antithrombins include, but are not limited to, sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor (available from Biogen located in Cambridge, Mass.), and 7E-3B.RTM. (An antiplatelet drug from Centocor located in Malvern, Pa.). Examples of antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycin. Examples of cytostatic or antiproliferative agents include angiopeptin (a somatostatin analog from Ibsen located in the United Kingdom), angiotensin converting enzyme inhibitors such as Captopril.RTM. (available from Squibb located in New York,

N.Y.), Cilazapril.RTM. (available from Hoffman-LaRoche located in Basel, Switzerland), or Lisinopril.RTM. (available from Merck located in Whitehouse Station, N.J.); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, Lovastatin.RTM. (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), methotrexate, monoclonal antibodies (such as PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available from GlaxoSmithKline located in United Kingdom), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic drugs or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, and dexamethasone.

[095] An anti-thrombosis agent, an anti-proliferate agent, an anti-inflammatory agent, especially rapamycin or paclitaxel and their analogues, as discussed above, can be used in combination with other drugs, such as inhaled corticosteroids, inhaled anticholinergics such as ipratropium and beta-agonists such as albuterol, inhaled leukotriene inhibitors, and inhaled epinephrine.

[096] Some drugs that are considered particularly suitable for the combination are inhaled corticosteroids such as, Budesonide, Flunisolide, Triamcinolone, Beclomethasone, Fluticasone, Mometasone, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisone, Cotisone, Betamethasone, or the like. Some other suitable drugs are bronchodilators such as Terbutaline, Albuterol, Ipratropium, Pirbuterol, Epinephrine, Salmeterol, Levalbuterol, Formoterol, or the like.

[097] Other drugs that are also considered to be suitably administered in the combinations include, but are not limited to, Leukotriene inhibitors such as Montelukast, Zafirlukast, Zileuton, or the like; antihistamines such as Loratadine, Cetirizine or the like; Anti-Tuberculosis drugs for M TB or atypical mycobacteria such as, Isoniazid, Ethambutol, Pyrazinamide, Rifamycin; Rifampin, Streptomycin, Clarithromycin, or the like; other drugs; such as the Serine lung protease inhibitors Azelastine, and Theophylline; and other peptides, such as those that relate to Allergy Immunotherapy for indoor and outdoor allergens, or the like. Additionally, amikacin, gentamicin, tobramicin, rifabutin, rifapentine, sparfloxacin, ciprofloxacin,

quinolones, azithromycin, erythromycin, isoniazid, or the like, can be considered to be useful.

[098] According to embodiments of the invention preferred, β_2 agonists in the combinations according to the invention are selected from the group consisting of albuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol , TD 3327, ritodrine, salmeterol, salmefamol, soterenot, sulphonterol, tiaramide, terbutaline, and tolubuterol.

Additive

[099] The additive according to embodiments of the present invention has two parts. One part is hydrophilic and the other part is a drug affinity part. The drug affinity part is a hydrophobic part, and/or has an affinity to the therapeutic agent by hydrogen bonding and/or van der Waals interactions. The drug affinity part of the additive may bind the hydrophobic or lipophilic drug, such as rapamycin or paclitaxel, with which they share structural similiraties, and lipids of cell membranes. The hydrophilic portion accelerates diffusion and increases permeation of the drug into tissue. In some embodiments, such as coatings for medical devices, the additive may facilitate rapid movement of drug off a medical device during deployment at the target site by preventing hydrophobic drug molecules from clumping to each other and to the device, increasing drug solubility in interstitial spaces, and/or accelerating drug passage through polar head groups to the lipid bilayer of cell membranes of target tissues.

[0100] The additive according to embodiments of the present invention has a drug affinity part and a hydrophilic part. The drug affinity part is a hydrophobic part and/or has an affinity to the therapeutic agent by hydrogen bonding and/or van der Waals interactions. The hydrophobic part may include aliphatic and aromatic organic hydrocarbon compounds, such as benzene, toluene, and alkanes, among others. These parts are not water soluble. They may bind both hydrophobic drug, with which they share structural similarities, and lipids of cell membranes. They have no covalently bonded iodine. The drug affinity part may include functional groups that can form hydrogen bonds with drug and with itself. The hydrophilic part may include hydroxyl groups, amine groups, amide groups, carbonyl groups,

carboxylic acid and anhydrides, ethyl oxide, ethyl glycol, polyethylene glycol, ascorbic acid amino acid, amino alcohol, glucose, sucrose, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic salts and their substituted molecules, among others. Hydroxyl, carboxyl, acid, amide or amine groups, for example, may be advantageous since they easily displace water molecules that are hydrogen-bound to polar head groups and surface proteins of cell membranes and may function to remove this barrier between hydrophobic drug and cell membrane lipid. These parts can dissolve in water and polar solvents. These additives are not oils, lipids, or polymers. The therapeutic agent is not enclosed in micelles or liposomes or encapsulated in polymer particles. The additive of embodiments of the present invention have hydrophobic and hydrophilic components to both bind drug and facilitate its rapid movement off a medical device during deployment and into target tissues.

[0101] The additives in embodiments of the present invention are surfactants and chemical compounds with one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester moieties. The surfactants include ionic, nonionic, aliphatic, and aromatic surfactants. The chemical compounds with one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester moieties are amino alcohols, hydroxyl carboxylic acid and anhydrides, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sugars, glucose, sucrose, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, and their substituted molecules.

[0102] As is well known in the art, the terms "hydrophilic" and "hydrophobic" are relative terms. To function as an additive in exemplary embodiments of the present invention, the compound includes polar or charged hydrophilic moieties as well as non-polar hydrophobic (lipophilic) moieties.

[0103] An empirical parameter commonly used in medicinal chemistry to characterize the relative hydrophilicity and hydrophobicity of pharmaceutical compounds is the partition coefficient, P, the ratio of concentrations of unionized compound in the two phases of a mixture of two immiscible solvents, usually octanol and water, such that P = ([solute]octanol / [solute]water). Compounds with higher log Ps are more hydrophobic, while compounds with lower log Ps are more hydrophilic. Lipinski's rule suggests that pharmaceutical compounds having log P < 5 are typically more membrane permeable. For purposes of certain embodiments

of the present invention, it is preferable that the additive has log P less than log P of the drug to be formulated (as an example, log P of paclitaxel is 7.4). A greater log P difference between the drug and the additive can facilitate phase separation of drug. For example, if log P of the additive is much lower than log P of the drug, the additive may accelerate the release of drug in an aqeous environment from the surface of a device to which drug might otherwise tightly adhere, thereby accelerating drug delivery to tissue. In certain embodiments of the present invention, log P of the additive is negative. In other embodiments, log P of the additive is less than log P of the drug. While a compound's octanol-water partition coefficient P or log P is useful as a measurement of relative hydrophilicity and hydrophobicity, it is merely a rough guide that may be useful in defining suitable additives for use in embodiments of the present invention.

[0104] Suitable additives that can be used in embodiments of the present invention include, without limitation, organic and inorganic pharmaceutical excipients, natural products and derivatives thereof (such as sugars, vitamins, amino acids, peptides, proteins, and fatty acids), low molecular weight oligomers, surfactants (anionic, cationic, non-ionic, and ionic), and mixtures thereof. The following detailed list of additives useful in the present invention is provided for exemplary purposes only and is not intended to be comprehensive. Many other additives may be useful for purposes of the present invention.

[0105] Surfactants

[0106] The surfactant can be any surfactant suitable for use in pharmaceutical compositions. Such surfactants can be anionic, cationic, zwitterionic or non-ionic. Mixtures of surfactants are also within the scope of the invention, as are combinations of surfactant and other additives. Surfactants often have one or more long aliphatic chains such as fatty acids that may insert directly into the lipid bilayers of cell membranes to form part of the lipid structure of the cells, while other components of the surfactants loosen the lipid structure and enhance drug penetration and absorption. The contrast agent, such as iopromide, does not have these properties.

[0107] An empirical parameter commonly used to characterize the relative hydrophilicity and hydrophobicity of surfactants is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more hydrophobic, and have

greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Using HLB values as a rough guide, hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, hydrophobic surfactants are compounds having an HLB value less than about 10.

[0108] It should be understood that the HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions, for example. For many important surfactants, including several polyethoxylated surfactants, it has been reported that HLB values can differ by as much as about 8 HLB units, depending upon the empirical method chosen to determine the HLB value (Schott, J. Pharm. Sciences, 79(1), 87-88 (1990)). Keeping these inherent difficulties in mind, and using HLB values as a guide, surfactants may be identified that have suitable hydrophilicity or hydrophobicity for use in embodiments of the present invention, as described herein.

[0109] PEG- Fatty Acids and PEG-Fatty Acid Mono and Diesters

[0110] Although polyethylene glycol (PEG) itself does not function as a surfactant, a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are most useful in embodiments of the present invention. Preferred hydrophilic surfactants include PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate and PEG-20 oleate. The HLB values are in the range of 4-20.

[0111] Polyethylene glycol fatty acid diesters are also suitable for use as surfactants in the compositions of embodiments of the present invention. Most preferred hydrophilic surfactants include PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate and PEG-32 dioleate. The HLB values are in the range of 5-15.

[0112] In general, mixtures of surfactants are also useful in embodiments of the present invention, including mixtures of two or more commercial surfactants as well as mixtures of surfactants with another additive or additives. Several PEG-fatty acid esters are marketed commercially as mixtures or mono- and diesters.

[0113] Polyethylene Glycol Glycerol Fatty Acid Esters

[0114] Preferred hydrophilic surfactants are PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, and PEG-30 glyceryl oleate.

[0115] Alcohol-Oil Transesterification Products

[0116] A large number of surfactants of different degrees of hydrophobicity or hydrophilicity can be prepared by reaction of alcohols or polyalcohol with a variety of natural and/or hydrogenated oils. Most commonly, the oils used are castor oil or hydrogenated castor oil, or an edible vegetable oil such as corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, or almond oil. Preferred alcohols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, and pentaerythritol. Among these alcohol-oil transesterified surfactants, preferred hydrophilic surfactants are PEG-35 castol oil (Incrocas 35), PEG 40 hydrogenated castor oil (Cremophor RH 40), PEG-25 trioleate (TAGAT.RTM. TO), PEG-60 corn glycerides (Crovol M70), PEG-60 almond oil (Crovol A70), PEG-40 palm kernel oil (Crovol PK70), PEG-50 castor oil (Emalex C-50), PEG-50 hydrogenated castor oil (Emalex HC-50), PEG-8 caprylic /capric glycerides (Labrasol), and PEG-5 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-9 hydrogenated castor oil, PEG-6 caprylic /capric glycerides (Softigen 767). Preferred hydrophobic surfactants in this class include PEG-6 corn oil (Labrafil.RTM. M 2125 CS), PEG-6 almond oil (Labrafil.RTM. M 1966 CS), PEG-6 apricot kernel oil (Labrafil.RTM. M 1944 CS), PEG-6 olive oil (Labrafil.RTM. M 1980 CS), PEG-6 peanut oil (Labrafil.RTM. M 1969 CS), PEG-6 hydrogenated palm kernel oil (Labrafil.RTM. M 2130 BS), PEG-6 palm kernel oil (Labrafil.RTM. M 2130 CS), PEG-6 triolein (Labrafil.RTM.b M 2735 CS), PEG-8 corn oil (Labrafil.RTM. WL 2609 BS), PEG-20 corn glycerides (Crovol M40), and PEG-20 almond glycerides (Crovol A40).

[0117] Polyglyceryl Fatty Acids

[0118] Polyglycerol esters of fatty acids are also suitable surfactants for use in embodiments of the present invention. Among the polyglyceryl fatty acid esters, preferred hydrophobic surfactants include polyglyceryl oleate (Plurol Oleique), polyglyceryl-2 dioleate (Nikkol DGDO), polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate. Preferred hydrophilic surfactants include polyglyceryl-10

laurate (Nikkol Decaglyn 1-L), polyglyceryl-10 oleate (Nikkol Decaglyn 1-O), and polyglyceryl-10 mono, dioleate (Caprol.RTM. PEG 860), polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate. Polyglyceryl polyricinoleates (Polymuls) are also preferred surfactants.

[0119] Propylene Glycol Fatty Acid Esters

[0120] Esters of propylene glycol and fatty acids are suitable surfactants for use in embodiments of the present invention. In this surfactant class, preferred hydrophobic surfactants include propylene glycol monolaurate (Lauroglycol FCC), propylene glycol ricinoleate (Propymuls), propylene glycol monooleate (Myverol P-O6), propylene glycol dicaprylate/dicaprate (Captex.RTM. 200), and propylene glycol dioctanoate (Captex.RTM. 800).

[0121] Sterol and Sterol Derivatives

[0122] Sterols and derivatives of sterols are suitable surfactants for use in embodiments of the present invention. Preferred derivatives include the polyethylene glycol derivatives. A preferred surfactant in this class is PEG-24 cholesterol ether (Solulan C-24).

[0123] Polyethylene Glycol Sorbitan Fatty Acid Esters

[0124] A variety of PEG-sorbitan fatty acid esters are available and are suitable for use as surfactants in embodiments of the present invention. Among the PEG-sorbitan fatty acid esters, preferred surfactants include PEG-20 sorbitan monolaurate (Tween-20), PEG-20 sorbitan monopalmitate (Tween-40), PEG-20 sorbitan monostearate (Tween-60), and PEG-20 sorbitan monooleate (Tween-80). In some embodiments, laurate esters are preferred because they have a short lipid compared with oleate esters, increasing drug absorption.

[0125] Polyethylene Glycol Alkyl Ethers

[0126] Ethers of polyethylene glycol and alkyl alcohols are suitable surfactants for use in embodiments of the present invention. Preferred ethers include PEG-3 oleyl ether (Volpo 3) and PEG-4 lauryl ether (Brij 30).

[0127] Sugar and Its Derivatives

[0128] Sugar derivatives are suitable surfactants for use in embodiments of the present invention. Preferred surfactants in this class include sucrose

monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, and octyl - β -D-thioglucopyranoside.

[0129] Polyethylene Glycol Alkyl Phenols

[0130] Several PEG-alkyl phenol surfactants are available, such as PEG-10-100 nonyl phenol and PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, and are suitable for use in embodiments of the present invention.

[0131] Polyoxyethylene-Polyoxypropylene (POE-POP) Block Copolymers

[0132] The POE-POP block copolymers are a unique class of polymeric surfactants. The unique structure of the surfactants, with hydrophilic POE and hydrophobic POP moieties in well-defined ratios and positions, provides a wide variety of surfactants suitable for use in embodiments of the present invention. These surfactants are available under various trade names, including Synperonic PE series (ICI); Pluronic.RTM. series (BASF), Emkalyx, Lutrol (BASF), Supronic, Monolan, Pluracare, and Plurodac. The generic term for these polymers is "poloxamer" (CAS 9003-11-6). These polymers have the formula: HO $(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$
where "a" and "b" denote the number of polyoxyethylene and polyoxypropylene units, respectively.

[0133] Preferred hydrophilic surfactants of this class include Poloxamers 108, 188, 217, 238, 288, 338, and 407. Preferred hydrophobic surfactants in this class include Poloxamers 124, 182, 183, 212, 331, and 335.

[0134] Sorbitan Fatty Acid Esters

[0135] Sorbitan esters of fatty acids are suitable surfactants for use in embodiments of the present invention. Among these esters, preferred hydrophobic surfactants include sorbitan monolaurate (Arlacel 20), sorbitan monopalmitate (Span-40), and sorbitan monooleate (Span-80), sorbitan monostearate.

[0136] The sorbitan monopalmitate, an amphiphilic derivative of Vitamin C (which has Vitamin C activity), can serve two important functions in solubilization

systems. First, it possesses effective polar groups that can modulate the microenvironment. These polar groups are the same groups that make vitamin C itself (ascorbic acid) one of the most water-soluble organic solid compounds available: ascorbic acid is soluble to about 30 wt/wt % in water (very close to the solubility of sodium chloride, for example). And second, when the pH increases so as to convert a fraction of the ascorbyl palmitate to a more soluble salt, such as sodium ascorbyl palmitate.

[0137] Ionic Surfactants

[0138] Ionic surfactants, including cationic, anionic and zwitterionic surfactants, are suitable hydrophilic surfactants for use in embodiments of the present invention. Preferred ionic surfactants include quaternary ammonium salts, fatty acid salts and bile salts. Specifically, preferred ionic surfactants include benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, edrophonium chloride, domiphen bromide, dialkylesters of sodium sulfonsuccinic acid, sodium dioctyl sulfosuccinate, sodium cholate, and sodium taurocholate. These quaternary ammonium salts are preferred additives. They can be dissolved in both organic solvents (such as ethanol, acetone, and toluene) and water. This is especially useful for medical device coatings because it simplifies the preparation and coating process and has good adhesive properties. Water insoluble drugs are commonly dissolved in organic solvents.

[0139] Chemical compounds with one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester moieties

[0140] The chemical compounds with one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester moieties include amino alcohols, hydroxyl carboxylic acid, ester, and anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sugars, glucose, sucrose, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acids, and their substituted molecules. Hydrophilic chemical compounds with one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide, or ester moieties having a molecular weight less than 5,000-10,000, are preferred in certain embodiments. In other embodiments, molecular weight of the additive with one or

more hydroxyl, amino, carbonyl, carboxyl, acid, amide, or ester moieties is preferably less than 1000-5,000, or more preferably less than 700-1,000, or most preferably less than 750. In these embodiments, molecular weight of the additive is preferred to be less than that of the drug to be delivered. Further, in some embodiments, the molecular weight of the additive is preferred to be higher than 80 since molecules with molecular weight less than 80 very easily evaporate and do not stay in coatings of a medical device. Small molecules can diffuse quickly. They can release themselves easily from the delivery balloon, accelerating release of drug, and they can diffuse away from drug when the drug binds tissue of the body lumen.

[0141] In certain embodiments, for example, in a coating for a medical device, more than four hydroxyl groups are preferred, for example in the case of a high molecular weight additive. Large molecules diffuse slowly. If the molecular weight of the additive or the chemical compound is high, for example if the molecular weight is above 800, above 1000, above 1200, above 1500, or above 2000; large molecules may elute off of the surface of a medical device too slowly to release drug under 2 minutes. If these large molecules contain more than four hydroxyl groups they have increased hydrophilic properties, which is necessary for relatively large molecules to release drug quickly. The increased hydrophilicity helps elute the coating off the balloon, accelerates release of drug, and improves or facilitates drug movement through water barrier and polar head groups of lipid bilayers to penetrate tissues. The hydroxyl group is preferred as the hydrophilic moiety because it is unlikely to react with water insoluble drug, such as paclitaxel or rapamycin. In some embodiments, the chemical compound having more than four hydroxyl groups has a melting point of 120°C or less. In some embodiments, the chemical compound having more than four hydroxyl groups has three adjacent hydroxyl groups that in stereo configuration are all on one side of the molecule. For example, sorbitol and xylitol have three adjacent hydroxyl groups that in stereoconfiguration are all on one side of the molecule, while galactitol does not. The difference impacts the physical properties of the isomers such as the melting temperature. The stereoconfiguration of the three adjacent hydroxyl groups may enhance drug binding. This will lead to improved compatibility of the water insoluble drug and hydrophilic additive, and improved tissue uptake and absorption of drug.

[0142] Some of the chemical compouds with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties described herein are very stable under heating. They survive an ethylene oxide sterilization process and do not react with the water insoluble drug paclitaxel or rapamycin during sterilization. L-ascorbic acid and its salt and diethanolamine, on the other hand, do not necessarily survive such a sterilization process, and they react with paclitaxel. A different sterilization method is therefore preferred for L-ascorbic acid and diethanolamine. Hydroxyl, ester, and amide groups are preferred because they are unlikely to react with therapeutic agents such as paclitaxel or rapamycin. Sometimes, amine and acid groups do react with paclitaxel, for example, experimentally, benzoic acid, gentisic acid, diethanolamine, and ascorbic acid were not stable under ethylene oxide sterilization, heating, and aging process and reacted with paclitaxel. When the chemical compounds described herein are formulated with paclitaxel, a top coat layer may be advantageous in order to prevent premature drug loss during the device delivery process before deployment at the target site, since hydrophilic small molecules sometimes release drug too easily. The chemical compounds herein rapidly elute drug off the balloon during deployment at the target site. Surprisingly, even though some drug is lost during transit of the device to the target site when the coating contains these additives, experimentally drug absorption by tissue is unexpectedly high after only 0.2-2 minutes of deployment, for example, with the additive hydroxyl lactones such as ribonic acid lactone and gluconolactone.

[0143] Fat-soluble Vitamins and Salts Thereof

[0144] Vitamins A, D, E and K in many of their various forms and provitamin forms are considered as fat-soluble vitamins and in addition to these a number of other vitamins and vitamin sources or close relatives are also fat-soluble and have polar groups, and relatively high octanol-water partition coefficients. Clearly, the general class of such compounds has a history of safe use and high benefit to risk ratio, making them useful as additives in embodiments of the present invention.

[0145] The following examples of fat-soluble vitamin derivatives and/or sources are also useful as additives: Alpha-tocopherol, beta-tocopherol, gamma-tocopherol, delta-tocopherol, tocopherol acetate, ergosterol, 1-alpha-hydroxycholecal- ciferol, vitamin D2, vitamin D3, alpha-carotene, beta-carotene, gamma-carotene, vitamin A, fursultiamine, methylolriboflavin, octotiamine,

prosultiamine, riboflavine, vintiamol, dihydrovitamin K1, menadiol diacetate, menadiol dibutyrate, menadiol disulfate, menadiol, vitamin K1, vitamin K1 oxide, vitamins K2, and vitamin K--S(II). Folic acid is also of this type, and although it is water-soluble at physiological pH, it can be formulated in the free acid form. Other derivatives of fat-soluble vitamins useful in embodiments of the present invention may easily be obtained via well known chemical reactions with hydrophilic molecules.

[0146] Water-soluble Vitamins and Their Amphiphilic Derivatives

[0147] Vitamins B, C, U, pantothenic acid, folic acid, and some of the menadione-related vitamins/provitamins in many of their various forms are considered water-soluble vitamins. These may also be conjugated or complexed with hydrophobic moieties or multivalent ions into amphiphilic forms having relatively high octanol-water partition coefficients and polar groups. Again, such compounds can be of low toxicity and high benefit to risk ratio, making them useful as additives in embodiments of the present invention. Salts of these can also be useful as additives in the present invention. Examples of water-soluble vitamins and derivatives include, without limitation, acetiamine, benfotiamine, pantothenic acid, cetotiamine, cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U. Also, as mentioned above, folic acid is, over a wide pH range including physiological pH, water-soluble, as a salt.

[0148] Compounds in which an amino or other basic group is present can easily be modified by simple acid-base reaction with a hydrophobic group-containing acid such as a fatty acid (especially lauric, oleic, myristic, palmitic, stearic, or 2-ethylhexanoic acid), low-solubility amino acid, benzoic acid, salicylic acid, or an acidic fat-soluble vitamin (such as riboflavin). Other compounds might be obtained by reacting such an acid with another group on the vitamin such as a hydroxyl group to form a linkage such as an ester linkage, etc. Derivatives of a water-soluble vitamin containing an acidic group can be generated in reactions with a hydrophobic group-containing reactant such as stearylamine or riboflavine, for

example, to create a compound that is useful in embodiments of the present invention. The linkage of a palmitate chain to vitamin C yields ascorbyl palmitate.

[0149] Amino Acids and Their Salts

[0150] Alanine, arginine, asparagines, aspartic acid, cysteine, cystine, glutamic acid, glutamine, glycine, histidine, proline, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tryptophan, tyrosine, valine, and their derivatives are other useful additives in embodiments of the invention.

[0151] Certain amino acids, in their zwitterionic form and/or in a salt form with a monovalent or multivalent ion, have polar groups, relatively high octanol-water partition coefficients, and are useful in embodiments of the present invention. In the context of the present disclosure we take "low-solubility amino acid" to mean an amino acid which has solubility in unbuffered water of less than about 4% (40 mg/ml). These include Cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine.

[0152] Amino acid dimers, sugar-conjugates, and other derivatives are also useful, such as dopamine hydrochloride, DOPA, LOVADOPA, and carbidopa. Through simple reactions well known in the art hydrophilic molecules may be joined to hydrophobic amino acids, or hydrophobic molecules to hydrophilic amino acids, to make additional additives useful in embodiments of the present invention.

[0153] Catecholamines, such as dopamine, levodopa, carbidopa, and DOPA, are also useful as additives.

[0154] Oligopeptides, Peptides and Proteins

[0155] Oligopeptides and peptides are useful as additives, since hydrophobic and hydrophilic amino acids may be easily coupled and various sequences of amino acids may be tested to maximally facilitate permeation of tissue by drug.

[0156] Proteins are also useful as additives in embodiments of the present invention. Serum albumin, for example, is a particularly preferred additive since it is water soluble and contains significant hydrophobic parts to bind drug: paclitaxel is 89% to 98% protein-bound after human intravenous infusion, and rapamycin is 92% protein bound, primarily (97%) to albumin. Furthermore, paclitaxel solubility in PBS increases over 20-fold with the addition of BSA. Albumin is naturally present at high concentrations in serum and is thus very safe for human intravascular use.

[0157] Other useful proteins include, without limitation, other albumins, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, and the like.

[0158] Organic Acids and Their Esters and Anhydrides

[0159] Examples are acetic acid and anhydride, benzoic acid and anhydride, acetylsalicylic acid, diflunisal, 2-hydroxyethyl salicylate, diethylenetriaminepentaacetic acid dianhydride, ethylenediaminetetraacetic dianhydride, maleic acid and anhydride, succinic acid and anhydride, diglycolic anhydride, glutaric anhydride, ascorbic acid, citric acid, tartaric acid, lactic acid, oxalic acid aspartic acid, nicotinic acid, 2-pyrrolidone-5-carboxylic acid, and 2-pyrrolidone.

[0160] These esters and anhydrides are soluble in organic solvents such as ethanol, acetone, methylethylketone, ethyl acetate. The water insoluble drugs can be dissolved in organic solvent with these esters and anhydrides, then coated easily on to the medical device, then hydrolyzed under high pH conditions. The hydrolyzed anhydrides or esters are acids or alcohols, which are water soluble and can effectively carry the drugs off the device into the vessel walls.

[0161] Other chemical compounds with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties

[0162] The additives according to embodiments include amino alcohols, alcohols, amines, acids, amides and hydroxyl acids in both cyclo and linear aliphatic and aromatic group. Examples are L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactrone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sorbitol, glucose, sucrose, lactose, maltose, ribose, arabinose, lyxose, xylose, fructose, mannose, glucitol, sugars, sugar phosphates, glucopyranose phosphate, sugar sulphates, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, xylitol, 2-ethoxyethanol, cyclodextrin, (2-hydroxypropyl)cyclodextrin, acetaminophen, ibuprofen, retinoic

acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine described, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof

[0163] .Combinations of additives are also useful for purposes of the present invention.

[0164] One embodiment comprises the combination or mixture of two additives, for example, a first additive comprising a surfactant and a second additive comprising a chemical compound with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties.

[0165] The combination or mixture of the surfactant and the small water-soluble molecule (the chemical compounds with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties) has advantages. Formulations comprising mixtures of the two additives with water-insoluble drug are in certain cases superior to mixtures including either additive alone. The hydrophobic drugs bind extremely water-soluble small molecules more poorly than they do surfactants. The water-insoluble drug has Log P higher than both that of the surfactant and that of small water-soluble molecules. However, Log P of the surfactant is typically higher than Log P of the chemical compounds with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties. The surfactant has a relatively high Log P (usually above 0) and the water soluble molecules have low Log P (usually below 0). Some surfactants, when used as additives in embodiments of the present invention, such as in coatings of medical devices, adhere so strongly to the water-insoluble drug and the surface of the medical device that drug is not able to rapidly release from the surface of the medical device at the target site. On the other hand, some of the water-soluble small molecules (with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties) adhere so poorly to the medical device that they release drug before it reaches the target site, for example, into serum during the transit of a coated balloon catheter to the site targeted for intervention. Suprisingly,

by adjusting the ratio of the concentrations of the small hydrophilic molecule and the surfactant in the formulation, the inventor has found that the coating stability during transit and rapid drug release when inflated and pressed against tissues of the lumen wall at the target site of therapeutic intervention in certain cases is superior to a formulation comprising either additive alone. Furthermore, the miscibility and compatibility of the water-insoluble drug and the highly water-soluble molecules is improved by the presence of the surfactant. The surfactant also improves coating uniformity and integrity by its good adhesion to the drug and the small molecules. The long chain hydrophobic part of the surfactant binds drug tightly while the hydrophilic part of the surfactant binds the water-soluble small molecules.

[0166] The surfactants in the mixture or the combination include all of the surfactants described herein for use in embodiments of the invention. The surfactant in the mixture may be chosen from PEG fatty esters, PEG omega-3 fatty esters and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, Tween 20, Tween 40, Tween 60, p-isononylphenoxypolyglycidol, PEG laurate, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate , PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, Tween 20, Tween 40, Tween 60, Tween 80, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside and their derivatives.

[0167] The chemical compound with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties in the mixture or the combination include all of the

chemical compounds with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties described herein for use in embodiments of the invention. The chemical compound with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties in the mixture has at least one hydroxyl group in one of the embodiments in the inventions. In certain embodiments, more than four hydroxyl groups are preferred, for example in the case of a high molecular weight additive. In some embodiments, the chemical compound having more than four hydroxyl groups has a melting point of 120°C or less. Large molecules diffuse slowly. If the molecular weight of the additive or the chemical compound is high, for example if the molecular weight is above 800, above 1000, above 1200, above 1500, or above 2000; large molecules may elute off of the surface of the medical device too slowly to release drug under 2 minutes. If these large molecules contain more than four hydroxyl groups they have increased hydrophilic properties, which is necessary for relatively large molecules to release drug quickly. The increased hydrophilicity helps elute the coating off the balloon, accelerates release of drug, and improves or facilitates drug movement through water barrier and polar head groups of lipid bilayers to penetrate tissues. The hydroxyl group is preferred as the hydrophilic moiety because it is unlikely to react with water insoluble drug, such as paclitaxel or rapamycin.

[0168] The chemical compound with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties in the mixture is chosen from L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sorbitol, glucitol sugar phosphates, glucopyranose phophate, sugar sulfates, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, xylitol, 2-ethoxyethanol, sugars, galactose, glucose, ribose, mannose, xylose, sucrose, lactose, maltose, arabinose, lyxose, fructose, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and

amine described above, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

[0169] Mixtures or combinations of a surfactant and a water-soluble small molecule confer the advantages of both additives. The water insoluble drug often has a poor compatibility with highly water-soluble chemical compounds, and the surfactant improves compatibility. The surfactant also improves the coating quality, uniformity, and integrity, and particles do not fall off the balloon during handling. The surfactant reduces drug loss during transit to a target site. The water-soluble chemical compound improves the release of drug off the balloon and absorption of the drug in the tissue. Experimentally, the combination was surprisingly effective at preventing drug release during transit and achieving high drug levels in tissue after very brief 0.2-2 minute deployment. Furthermore, in animal studies it effectively reduced stenosis and late lumen loss.

[0170] Some of the mixtures or combinations of surfactants and water-soluble small molecules are very stable under heating. They survived an ethylene oxide sterilization process and do not react with the water insoluble drug paclitaxel or rapamycin during sterilization. The hydroxyl, ester, amide groups are preferred because they are unlikely to react with therapeutic agents such as paclitaxel or rapamycin. Sometimes amine and acid groups do react with paclitaxel and are not stable under ethylene oxide sterilization, heating, and aging. When the mixtures or combinations described herein are formulated with paclitaxel, a top coat layer may be advantageous in order to protect the drug layer and from premature drug loss during the device.

[0171] Preferred additives include p-isononylphenoxypolyglycidol, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG

sorbitan stearate, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine (amino acids); cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid and its salt, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U (vitamins); albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, , glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations

thereof.(chemical compounds with one or more hydroxyl, amino, carbonyl, carboxyl, or ester moieties). Some of these additives are both water-soluble and organic solvent-soluble. They have good adhesive properties and adhere to the surface of polyamide medical devices, such as balloon catheters. They may therefore be used in the adherent layer, top layer, and/or in the drug layer of embodiments of the present invention. The aromatic and aliphatic groups increase the solubility of water insoluble drugs in the coating solution, and the polar groups of alcohols and acids accelerate drug permeation of tissue.

[0172] Other preferred additives in embodiments of the invention include the combination of a surfactant and a chemical compounds with one or more hydroxyl, amine, carbonyl, carboxyl, or ester moieties. Examples are Tween 20/sorbitol, Tween 20/glucose, Tween 20/sucrose, Tween 20/lactobionic acid, Tween 20/gluconolactone, Tween 20/meglumine/lactic acid, Tween 20/meglumine/gentisic acid, Tween 80/sorbitol, Tween 80/glucose, Tween 80/sucrose, Tween 80/lactobionic acid, Tween 80/gluconolactone, Tween 80/meglumine/lactic acid, Tween 80/meglumine/gentisic acid, N-octanoyl N-methylglucamine/sorbitol, N-octanoyl N-methylglucamine/glucose, N-octanoyl N-methylglucamine/sucrose, N-octanoyl N-methylglucamine/lactobionic acid, N-octanoyl N-methylglucamine/gluconolactone, N-octanoyl N-methylglucamine/meglumine/lactic acid, and N-octanoyl N-methylglucamine/meglumine/gentisic acid.

[0173] Other preferred additives according to embodiments of the invention include the combination or mixture or amide reaction products of an amino alcohol and an organic acid. Examples are lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, and acetic acid/diethanolamine.

[0174] Other preferred additives according to embodiments of the invention include hydroxyl ketone, hydroxyl lactone, hydroxyl acid, hydroxyl ester, and hydroxyl amide. Examples are gluconolactone, D-glucoheptono-1, 4-lactone,

glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucuronic acid, gluconic acid, gentisic acid, lactobionic acid, lactic acid, acetaminophen, vanillic acid, sinapic acid, hydroxybenzoic acid, methyl paraben, propyl paraben, and derivatives thereof.

[0175] Other preferred additives include n-octyl- β -D-glucopyranoside, octoxynol-9 (Triton X-100), Polysorbates (such as 20, 21, 40, 60, 80 and 81), Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol (Olin-10 G and Surfactant-10G), PEG glyceryl monooleate, sorbitan monolaurate (Arlacel 20), sorbitan monopalmitate (Span-40), sorbitan monooleate (Span-80), sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, L-ascorbic acid, thiamine, maleic anhydride, niacinamide, 2-pyrrolidone-5-carboxylic acid, and the like. These additives are both water soluble and organic solvent soluble. They have good adhesive properties and adhere to the surface of polyamide medical devices, such as balloon catheters. They may therefore be used in both the adherent layer and in the drug layer of embodiments of the present invention. The aromatic and aliphatic groups increase the solubility of water insoluble drugs in the coating solution, and the polar groups of alcohols and acids accelerate drug permeation of tissue.

[0176] Other preferred additives that may be useful in embodiments of the present invention include riboflavin, riboflavin-phosphate sodium, Vitamin D3, folic acid (vitamin B9), vitamin 12, diethylenetriaminepentaacetic acid dianhydride, ethylenediaminetetraacetic dianhydride, maleic acid and anhydride, succinic acid and anhydride, diglycolic anhydride, glutaric anhydride, L-ascorbic acid, thiamine, nicotinamide, nicotinic acid, 2-pyrrolidone-5-carboxylic acid, cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine.

[0177] From a structural point of view, these additives share structural similarities and are compatible with water insoluble drugs (such as paclitaxel and rapamycin). They often contain double bonds such as C=C, C=N, C=O in aromatic or aliphatic structures. These additives also contain amine, alcohol, ester, amide, anhydride, carboxylic acid, and/or hydroxyl groups. They may form hydrogen bonds and van der Waals interactions with drug. Compounds containing one or more hydroxyl, carboxyl, or amine groups, for example, are especially useful as additives

because these additives have a good affinity to the vessel wall. These molecules are polyglyceryl fatty esters, ascorbic ester of fatty acids, sugar ester, alcohol and ether of fatty acids. The fatty chains can insert into the lipid structure of target tissue membranes carrying drug to lipid structures. Some of the amino acids, vitamins and organic acids have aromatic C=N groups as well as amino, hydroxyl, and carboxylic components to their structure. These structure can bind or complex with hydrophobic drug, such as paclitaxel or rapamycin, and they also have structural parts that facilitate tissue penetration by removing barriers between hydrophobic drug and lipid structure of cell membranes.

[0178] For example, isononylphenylpolyglycidol (Olin-10 G and Surfactant-10G), PEG glyceryl monooleate, sorbitan monolaurate (Arlacel 20), sorbitan monopalmitate (Span-40), sorbitan monooleate (Span-80), sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, and polyglyceryl-10 stearate all have more than four hydroxyl groups in their hydrophilic part. These hydroxyl groups have very good affinity to the vessel wall and can displace hydrogen bound water molecules. At the same time they have long chains of fatty acid, alcohol, ether and ester that can both complex with hydrophobic drug and integrate into the lipid structure of the cell membranes to form the part of the lipid structure. This deformation or loosening of the lipid membrane of target cells may further accelerate permeation of hydrophobic drug into tissue.

[0179] For another example, L-ascorbic acid, thiamine, maleic acids, niacinamide, and 2-pyrrolidone-5-carboxylic acid, all have a very high water and ethanol solubility and a low molecular weight and small size; therefore they can penetrate into the tissue easily. They also have structural coponents including aromatic C=N, amino, hydroxyl, and carboxylic groups. These structures have very good compatibility with paclitaxel and rapamycin and can increase the solubility of the water-insoluble drugs in water and enhance their absorption into tissues.

[0180] Representative examples of additives include cetyl pyridinium chloride, gelatin, casein, lecithin (phosphatides), dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens.RTM. such as

e.g., Tween 20.RTM. and Tween 80.RTM. (ICI Specialty Chemicals)); polyethylene glycols (e.g., Carbowaxs 3350.RTM. and 1450.RTM., and Carbopol 934.RTM. (Union Carbide)), dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl cellulose (HPC, HPC-SL, and HPC-L), hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronics F68.RTM. and F108.RTM., which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic 908.RTM., also known as Poloxamine 908.RTM., which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); a charged phospholipid such as dimyristoyl phophatidyl glycerol, dioctylsulfosuccinate (DOSS); Tetronic 1508.RTM. (T-1508) (BASF Wyandotte Corporation), dialkylesters of sodium sulfosuccinic acid (e.g., Aerosol OT.RTM., which is a dioctyl ester of sodium sulfosuccinic acid (American Cyanamid)); Duponol P.RTM., which is a sodium lauryl sulfate (DuPont); Tritons X-200.RTM., which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110.RTM., which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-10G.RTM. or Surfactant 10-G.RTM. (Olin Chemicals, Stamford, Conn.); Crodestas SL-40.RTM. (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; and the like. Tyloxapol is a particularly preferred additive

for the pulmonary or intranasal delivery of steroids, even more so for nebulization therapies.

[0181] Some of the additives are characterized by rapid extracellular distribution followed by renal excretion by glomerular filtration. It has been reported (*Topic in Current Chemistry, Vol. 222, P 150*) that these additives are extravasated to a massive extent on the first pass and extraction of the nonionic additives averaged 33% in normally perfused myocardial area and 50% in stenotic area. In another model, approximately 80% of the myocardial content of I-iothalamate was found in the extravascular space 1 minute after intravenous injection in rats.

[0182] Some of the X-ray contrast agents can be used as the additives in embodiments of the invention. Iodinated contrast agents are widely used in X-ray diagnostic procedure such as angiography, urography and computed tomography. X-ray contrast agents have been moved historically from inorganic iodide, to organic mono-iodine compounds (Uroselectan A), bis-iodine (Uroselectan B) and tris-iodine substances (diatrizoate), from lipophilic to hydrophilic agents from ionic (diatrizoate) to non-ionic drugs (iopromide) and from monomers (iopromide) to dimmers (iotrolan).

[0183] All presented available X-ray contrast agents for intravascular injection are based upon the triiodobenzene ring substituted with two or three additional hydrophilic groups. In the case of biliary contrast agents (compounds that are taken up by the liver and excreted mainly by the biliary tract), two hydrophilic groups are introduced. For angiographic/urographic agents (compounds that stay within the extravascular distribution volume and that are excreted by the kidneys), three hydrophilic groups are introduced. The monomers are exclusively derived from aminoisophathalic acid. They only differ by their side-chains, which determine their physiochemical characteristics such as solubility, hydrophilicity, viscosity and osmolality. The aqueous solubility of X-ray contrast agents is generally extremely high being in the order of 1000 mg/ml. Most preparations of X-ray contrast agents are over-saturated solutions.

[0184] The relative amount of drug and additive can vary widely and the optimal amount of the additive can depend upon, for example, the particular drug and additives selected, the critical micelle concentration of the additive if it forms micelles, the hydrophilic-lipophilic-balance (HLB) of the additive, the melting point of

the additive, the water solubility of the additive and/or drug, the surface tension of water solutions of the additive, etc.

[0185] In embodiments of the present invention, the optimal ratio of drug to additive is about 1% to about 99% drug, more preferably about 30% to about 90% drug.

[0186] Adherent Layer

[0187] The adherent layer, which is an optional layer underlying the drug coating layer, improves the adherence of the drug coating layer to the exterior surface of the medical device, such as a balloon catheter or stent, and protects coating integrity. If drug and additive differ in their adherence to the medical device, the adherent layer may prevent differential loss (during transit) or elution (at the target site) of drug layer components in order to maintain consistent drug-to-additive ratio delivery at the target site of therapeutic intervention. Furthermore, the adherent layer may function to facilitate release of coating layer components which otherwise might adhere too strongly to the device for elution during brief contact with tissues at the target site. For example, in the case where a particular drug binds the medical device tightly, more hydrophilic components are incorporated into the adherent layer in order to decrease affinity of the drug to the device surface.

[0188] The adherent layer comprises a polymer or an additive or mixtures of both. The polymers that are useful for forming the adherent layer are ones that are biocompatible and avoid irritation of body tissue. Some examples of polymers that are useful for forming the adherent layer are polymers that are biostable, such as polyurethanes, silicones, and polyesters. Other polymers that are useful for forming the adherent layer include polymers that can be dissolved and polymerized on the medical device.

[0189] Some examples of polymers that are useful in the adherent layer of embodiments of the present invention include polyolefins, polyisobutylene, ethylene-α-olefin copolymers, acrylic polymers and copolymers, polyvinyl chloride, polyvinyl methyl ether, polyvinylidene fluoride and polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polystyrene, polyvinyl acetate, ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, Nylon 12 and its block copolymers, polycaprolactone, polyoxymethylenes, polyethers, epoxy resins, polyurethanes, rayon-triacetate, cellulose, cellulose acetate, cellulose

butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose, chitins, polylactic acid, polyglycolic acid, polylactic acid-polyethylene oxide copolymers, polyethylene glycol, polypropylene glycol, polyvinyl alcohol, and mixtures and block copolymers thereof.

[0190] Since medical devices such as balloon catheters and stents undergo mechanical manipulation, i.e., expansion and contraction, examples of polymers that are useful in the adherent layer include elastomeric polymers, such as silicones (e.g., polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers. Due to the elastic nature of these polymers, when these polymers are used, the coating better adheres to the surface of the medical device when the device is subjected to forces or stress.

[0191] The adherent layer may also comprise one or more of the additives previously described, or other components, in order to maintain the integrity and adherence of the coating layer to the device and to facilitate both adherence of drug and additive components during transit and rapid elution during deployment at the site of therapeutic intervention.

[0192] Top Layer

[0193] In order to further protect the integrity of the drug layer, an optional top layer may be applied to prevent loss of drug during transit through tortuous anatomy to the target site or during the initial expansion of the device before the coating makes direct contact with target tissue. The top layer may release slowly in the body lumen while protecting the drug layer. The top layer will erode more slowly if it is comprised of more hydrophobic, high molecular weight additives. Surfactants are examples of more hydrophobic structures with long fatty chains, such asTween 20 and polyglyceryl oleate. High molecular weight additives include polyethylene oxide, polyethylene glycol, and polyvinyl pyrrolidone. Hydrophobic drug itself can act as a top layer component. For example, paclitaxel or rapamycin are hydrophobic. They can be used in the top layer. On the other hand, the top layer cannot erode too slowly or it might actually slow the release of drug during deployment at the target site. Other additives useful in the top coat include additives that strongly interact with drug or with the coating layer, such as p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG

oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl

paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

[0194] In asthma and COPD, many of the clinical signs and symptoms are due to airway obstruction resulting from smooth muscle constriction. The magnitude of the obstructive response observed for a given degree of smooth muscle activation reflects the contractile capacity of the airway smooth muscle and the resistance to airway deformation. The airway smooth muscle plays a central role in asthma. The luminal folding or buckling as a consequence of airway smooth muscle constriction has been observed in asthma. Such bucking has also been observed in arteries, blood vessels in the myocardium, and the gastrointestinal tract (*J. Appl. Physiol. 83(6): 1814—1821, 1977*). Studies also show that airway smooth muscle cell, in addition to its contractile function, can participate in and coordinate the inflammatory response. The inflammatory smooth muscle produces excess thick and sticky mucus, which causes asthma attack by blocking airways. The smooth muscle hyperplasia has been linked to airway hyper responsiveness that is a critical phenotypic characteristic of asthma.

[0195] The causes of the coronary heart diseases and asthma may be the neointimal proliferation of smooth muscle in arterial vessels and in walls of airways. The one aspect of the invention is to deliver paclitaxel or rapamycin and their analogues to the wall of airways to treat the asthma. The drug coated stents with the two drugs have been approved for inhibiting the growth of the smooth muscle cells in vascular arterial vessels. Drug coated balloon has been approved to achieve similar results as the drug coated stent. Therefore, the drug coated stent and drug coated balloon used for vascular diseases can be adapted in the obstructive airway for the treatment of asthma. The method comprises inserting the therapeutic- agent- delivery balloon catheter into the airway in the lung, inflating the

balloon catheter, releasing drug to an airway wall of an airway such that a diameter of the airway is increased, deflating the balloon, withdrawing the balloon catheter from the airway. The drug may be released to the airway wall prior to, during, or after an asthma attack. The drug may be released in an amount sufficient to temporarily or permanently increase the diameter of the airway. The method may be performed while the airway is open, closed, or partially closed.

[0196] The pulmonary balloon catheters and stents are similar to vascular balloon catheters and stents. The diameters of the pulmonary balloon catheters and stents are 8, 10, 12, 14, 16, 18, 20, 22 mm with lengths of 20, 30, 40, 50, 60, 70, 80 mm. It is designed to pass over a 0.035 in guide wire through its guide wire lumen. The balloon can also be passed through a minimum 5.0mm working channel bronchoscope. The diameters of the sinus balloon catheters are 2.0, 3.0, 3.0, 4.0 mm and 10 mm with lengths of 10, 12, 15, 18, 20, and 30 mm.

[0197] The paclitaxel or rapamycin and their analogues can be used for treatments of respiratory disorders such as asthma, chronic obstructive pulmonary disease and chronic sinusitis. A method of treating respiratory disorders comprises administrating an anti-proliferate and anti- inflammatory effective amount of rapamycin, or paclitaxel or their analogues to said mammal orally, parenterally, intravascularly, intranasally, intrabronchially, transdermally, rectally, or via an impregnated vascular stent or balloon catheters.

[0198] The paclitaxel or rapamycin and their analogues can be used in combinations with inhaled corticosteroids, inhaled atrovent, inhaled leukotriene inhibitors, and inhaled epinephrine, long acting & selective beta agonists for treatments of asthma and COPD. A method of treating asthma and COPD in the lung comprises administrating an anti-proliferate and anti-inflammatory effective amount of rapamycin, or paclitaxel or their analogues in combinations with inhaled corticosteroids, inhaled atrovent, inhaled leukotriene inhibitors, inhaled epinephrine, long acting & selective beta agonists to said mammal orally, parenterally, intravascularly, intranasally, intrabronchially, transdermally, rectally, or via an impregnated vascular stent or balloon catheters.

[0199] Embodiments of the present invention also pertain to a method for treating the disease state, especially nasal and sinus dysplasia in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response and

compositions useful in the method. The method for treating the disease state in mammals caused by mammalian nasal and sinus cells involved in the inflammatory response comprises: contacting the mammalian nasal and sinus cells participating in the inflammatory response with the anti-proliferate and anti- inflammatory drugs.

[0200] Embodiments of the present invention also pertain to compositions for reducing and treating the disease state in mammals caused by undesired inflammatory response of nasal and sinus cells comprising an anti-proliferate and anti- inflammatory drug a carrier, and an additive composition, wherein the drugs are paclitaxel, rapamycin and their analogues.

[0201] In a preferred embodiment, the therapeutic compositions are administered by nasal inhalation. In another preferred embodiment, the therapeutic compositions are administered by nose drops. The therapeutic compositions may be first nebulized by any suitable means. The therapeutic compositions may be in liquid or solid form with liquid droplets or particle size being small enough to facilitate access to nasal and sinus tissue by inhalation or nose drops.

[0202] In one embodiment, the ratio by weight of the additive to the therapeutic agent in the layer is from about 0.05 to 100, for example, from about 0.1 to 5, from 0.5 to 2, and further for example, from about 0.8 to 1.2.

[0203] Although various embodiments are specifically illustrated and described herein, it will be appreciated that modifications and variations of the present invention are covered by the above teachings and are within the purview of the appended claims without departing from the spirit and intended scope of the invention.

[0204] **EXAMPLES**

[0205] The following examples include embodiments of formulations and medical device coating layers within the scope of the present invention. The examples presented here are all vascular applications. The pathological structure of blood vessels and airway and sinus lumen are very similar. All of the layer structure and cell types are very similar as well. The drug formulation, device and drug absorption can be applied in the treatment of asthma, chronic obstructive pulmonary disease, and chronic sinusitis. While the following examples are considered to embody the present invention, the examples should not be interpreted as limitations upon the present invention.

[0206] Example 1.

[0207] Preparation of coating solutions:

[0208] **Formulation 1**-50-150 mg (0.06-0.18 mmole) paclitaxel, 2-6 ml acetone (or ethanol), 25-100 mg ascorbyl palmitate, 25-100 mg L-ascorbic acid and 0.5 ml ethanol were mixed.

[0209] **Formulation 2**-50-150 mg (0.05-0.16 mmole) rapamycin, 2-6 ml acetone (or ethanol), 50-200 mg polyglyceryl-10 oleate and 0.5 ml ethanol were mixed.

[0210] **Formulation 3**-50-150 mg (0.06-0.18 mmole) paclitaxel, 2-6 ml acetone (or ethanol), 50-200 mg octoxynol-9 and 0.5 ml ethanol were mixed.

[0211] **Formulation 4**-50-150 mg (0.05-0.16 mmole) rapamycin, 2-6 ml acetone (or ethanol), 50-200 mg p-isononylphenoxypolyglycidol and 0.5 ml ethanol were mixed.

[0212] **Formulation 5**-50-150 mg (0.06-0.18 mmole) paclitaxel, 2-6 ml acetone (or ethanol), 50-200 mg Tyloxapol and 0.5 ml ethanol was mixed.

[0213] **Formulation 6**-50-150 mg (0.05-0.16 mmole) rapamycin in 2-6 ml acetone (or ethanol), 50-150 mg L-ascorbic acid in 1 ml water or ethanol, both, then were mixed.

[0214] **Formulation 7**-50-150 mg (0.06-0.18 mmole) paclitaxel, 2-6 ml acetone (or ethanol), 50-150 mg niacinamide in 1 ml water or ethanol, and both were mixed.

[0215] **Formulation 8**--50-150 mg (0.05-0.16 mmole) rapamycin, 2-6 ml acetone (or ethanol), 50-200 mg nicotinic acid in 1 ml water or ethanol and both were mixed.

[0216] **Formulation 9**-50-150 mg (0.06-0.18 mmole) paclitaxel, 2-6 ml ethanol (or acetone), 150 mg thiamine hydrochloride in 1 ml water, and 0.5 ml both were mixed.

[0217] **Formulation 10**-50-150 mg (0.05-0.16 mmole) rapamycin, 2-6 ml acetone or ethanol , 150 mg 2-pyrrolidone-5-carboxylic acid in 1 ml water or ethanol, and both were mixed.

[0218] **Formulation 11**-50-150 mg (0.06-0.18 mmole) paclitaxel, 2-6 ml acetone (or ethanol), 75 mg p-isononylphenoxypolyglycidol, 75 mg niacinamide in 1 ml water or ethanol, and 0.5 ml ethanol were mixed.

[0219] **Formulation 12**-50-150 mg (0.05-0.16 mmole) rapamycin, 2-6 ml acetone (or ethanol), 75 mg Octoxynol-9, 75 mg thiamine hydrochloride in 1 ml water or ethanol, and 0.5 ml ethanol were mixed.

[0220] **Formulation 13**-50-150 mg (0.06-0.18 mmole) paclitaxel, 2-6 ml acetone (or ethanol), 75 mg p-isononylphenoxypolyglycidol, 75 mg 2-pyrrolidone-5-carboxylic acid in 1 ml water or ethanol , and 0.5 ml ethanol were mixed.

[0221] **Formulation 14**-50-150 mg (0.06-0.18 mmole) paclitaxel, 2-6 ml acetone (or ethanol), 75 mg p-isononylphenoxypolyglycidol, 75 mg nicotinic acid in 1 ml water or ethanol , and 0.5 ml ethanol were mixed.

[0222] **Formulation 15** 50-150 mg (0.06-0.18 mmole) paclitaxel, 2-6ml acetone (or ethanol), 75 mg p-isononylphenoxypolyglycidol, 75 mg L-ascorbic acid in 1 ml water or ethanol , and 0.5 ml ethanol were mixed.

[0223] **Formulation 16** 50-150 mg (0.06-0.18 mmole) paclitaxel was dissolved in 5-10 ml methylene chloride. The solution was added to 30 ml of human serum albumin solution (5%w/v). The solution was then homogenized for 5 minutes at low speed to form an emulsion. The emulsion was then sonicated at 40 kHz at 50-90% power at 0 to 5 degrees C for 1 to 5 min.

[0224] **Formulation 17**-50-150 mg (0.05-0.16 mmole) rapamycin was dissolved in 5-10 ml methylene chloride and 10-30 mg p-isononylphenoxypolyglycidol. The solution was added to 30 ml of human serum albumin solution (5%w/v). The solution was then homogenized for 5 minutes at low speed to form an emulsion. The emulsion was then sonicated at 40 kHz at 50-90% power at 0 to 5° C for 1 to 5 min.

[0225] **Formulation 18**-50-100 mg (0.06-0.12 mmmole) paclitaxel, 1-1.6 ml acetone, 1-1.6 ml ethanol, 0.4-1.0 ml water, and 50-200 mg gluconolactone were mixed.

[0226] **Formulation 19**-35-70 mg (0.042-0.084 mmmole) paclitaxel, 0.5-1.0 ml acetone, 0.5-1.0 ml ethanol, 35-70 mg Tween 20, and 35-70 mg N-octanoyl N-methylglucamine were mixed.

[0227] **Formulation 20**-35-70 mg (0.042-0.084 mmmole) paclitaxel, 0.4-1.0 ml acetone, 0.4-1.0 ml ethanol, 0.2-0.4 ml water, 35-70 mg Tween 20, and 35-70 mg sorbitol were mixed.

[0228] **Formulation 21**-40-80 mg (0.048-0.096 mmmole) paclitaxel, 0.5-1.0 ml acetone, 0.5-1.0 ml ethanol, 40-80 mg meglumine, and 32-64 mg gensitic acid (equal molar ratio with meglumine) were mixed.

[0229] **Formulation 22**-35-70 mg (0.042-0.084 mmmole) paclitaxel, 0.4-0.8 ml acetone, 0.4-0.8 ml ethanol, 0.25-0.50 ml water, 35-70 mg lactobionic acid, and 10-20 mg diethanolamine (equal molar ratio with lactobionic acid) were mixed.

[0230] **Formulation 23**-35-70 mg (0.042-0.084 mmmole) paclitaxel, 0.5-1.0 ml acetone, 0.5-1.0 ml ethanol, and 70-140 mg N-octanoyl N-methylglucamine were mixed.

[0231] **Formulation 24**-35-70 mg (0.042-0.084 mmmole) paclitaxel, 0.4-0.8 ml acetone, 0.4-0.8 ml ethanol, 0.2-0.4 ml water, 35-70 mg meglumine, and 18-36 mg lactic acid (equal molar ratio with meglumine) were mixed.

[0232] **Formulation 25**-50-100 mg (0.06-0.12 mmole) paclitaxel, 0.8-1.6 ml acetone, 0.8-1.6 ml ethanol, 0.4-1.0 ml water, 50-100 mg gensitic acid, and 30-60 mg diethanolamine (equal molar ratio with gensitic acid) were mixed.

[0233] **Formulation 26**-Comparison solution-50 mg (0.06 mmole) paclitaxel, 1 ml ethanol, 0.2 ml acetone, 0.042 ml Ultravist 370 were mixed.

[0234] **Formulation 27**-Comparison solution-40 mg (0.048 mmole) paclitaxel, 0.5 ml ethanol, 0.5 ml acetone were mixed.

[0235] **Formulation 28**-35-70 mg (0.042-0.084 mmmole) paclitaxel, 0.5-1.0 ml acetone, 0.5-1.0 ml ethanol, 35-70 mg Triton X-100, and 35-70 mg N-heptanoyl N-methylglucamine were mixed.

[0236] Example 2

[0237] 5 PTCA balloon catheters (3 mm in diameter and 20 mm in length) were folded with three wings under vacuum. The folded balloon under vacuum was sprayed or dipped in a formulation (1-17) in example 1. The folded balloon was then dried, sprayed or dipped again, dried again, and sprayed or dipped again until sufficient amount of drug on the balloon (3 microgram per square mm) was

obtained. The coated folded balloon was then rewrapped and sterilized for animal testing.

[0238] Example 3

[0239] 5 PTCA balloon catheters (3 mm in diameter and 20 mm in length) were folded with three wings under vacuum. The folded balloon under vacuum was sprayed or dipped in a formulation (1-5) in example 1. The folded balloon was then dried, sprayed or dipped again in a formulation (6-10), dried, and sprayed or dipped again until sufficient amount of drug on the balloon (3 microgram per square mm) is obtained. The coated folded balloon was then rewrapped and sterilized for animal testing.

[0240] Example 4

[0241] 5 PTCA balloon catheters crimped with bare metal coronary stent (3 mm in diameter and 20 mm in length) were sprayed or dipped in a formulation (1-5) in example 1. The stent delivery system was then dried, sprayed or dipped again in a formulation (6-10), dried and sprayed or dipped again until sufficient amount of drug on the stent and balloon (3 microgram per square mm) was obtained. The coated folded stent delivery system was then sterilized for animal testing.

[0242] Example 5

[0243] Drug coated balloon catheters and uncoated balloon catheters (as control) were inserted into coronary arteries in pigs. The balloon was over dilated (1:1.2), and the inflated balloon was held in the vessel for 60 seconds to release drug, then deflated and withdraw from the pig. The animals were angiographed after 3 days, 31 days, 3 months, 6 months, 9 months and 12 months. The amount of drug in the artery tissues of the sacrificed animal was measured after 60 minutes, 3 days, 31 days, 3 months, 6 months, 9 months and 12 months.

[0244] Example 6

[0245] 5 coronary stents (3 mm in diameter and 18 mm in length) were spray or dip coated with the formulation (1-17) in example 1. The stents were then dried,

sprayed or dipped again, and dried again until a sufficient amount of drug on the stent (3 microgram per square mm) is obtained. The coated stent was then crimped on PTCA balloon catheters (3 mm in diameters and 20 mm in length). The coated stents with balloon catheters were then sterilized for animal testing.

[0246] Example 7

[0247] The drug coated stent and uncoated stent (as control) were inserted into coronary arteries in pigs, then the balloon is over dilated (1:1.2). The stent was implanted and drug released, and the balloon is deflated and withdraws from the pig. The animals were then angiographed after 5, 30, 60 minutes, 3 days, 31 days, 3 months, 6 months, 9 months and 12 months. The amount of drug in the artery tissues of the sacrificed animal was measured 60 minutes, 1 day, 3 days, 31 days, 3 months, 6 months, 9 months and 12 months.

[0248] Example 8

[0249] 5 PTCA balloon catheters were sprayed or dipped in the formulation (1-17) in example 1, dried, and sprayed or dipped and dried again until sufficient amount of drug on balloon iwasobtained (3 microgram per square mm) was obtained. A bare metal coronary stent (3 mm in diameter and 20 mm in length) was crimped on each coated balloon. The coated balloons with crimped bare metal stents was then wrapped and sterilized for animal test.

[0250] Example 9

[0251] 5 PTCA balloon catheters were sprayed or dipped in a formulation (1-5) in example 1, dried, and sprayed or dipped again in a formulation (6-10). Balloons were then dried and sprayed or dipped again until sufficient amount of drug on the balloon (3 microgram per square mm) was obtained. A bare metal coronary stent (3 mm in diameter and 20 mm in length) was crimped on each coated balloon. The coated balloons with crimped bare metal stents were then wrapped and sterilized for animal test.

[0252] Example 10

[0253] The drug coated balloon-expandable bare metal stent of Example 8 and 9 and plain balloon-expandable bare metal stent (as control) were inserted into coronary arteries in pigs, and the balloon is over dilated (1:1.2). Stent was implanted, and the balloon is held inflated for 60 seconds to release drug, and the balloon was deflated and withdraw from the pig. The animals were then angiographed after 5, 30, 60 minutes, 3 days, 31 days, 3 months, 6 months, 9 months and 12 months. The amount of drug in the artery tissues of the sacrificed animal was measured after 60 minutes, 1 day, 3 days, 31 days, 3 months, 6 months, 9 months and 12 months.

[0254] Example 11

[0255] 150 mg (0.18 mmole) paclitaxel, 5 ml acetone (or ethyl acetate or methyl ethyl ketone), 150 mg acetic anhydride or maleic anhydride or diglycolic anhydride and 0.5 ml ethanol were mixed, then stirred until a solution was obtained. 5 PTCA balloon catheters are sprayed or dipped in the solution, dried, and sprayed or dipped again until sufficient amount of drug on the balloon (3 microgram per square mm) was obtained. The coated balloon was then treated under high pH (range pH 8-11.5) conditions to hydrolyze the anhydride. This was confirmed by IR method. The hydrophilicity of the coating was increased. The coated balloons were then sterilized for animal test.

[0256] Example 12

[0257] The drug coated balloon catheters and uncoated balloon catheters (as control) were inserted via a bronchoscope into the pulmonary airway in pigs. The balloon was dilated, and the inflated balloon was held expanded in the lumen for 60 seconds to release drug. The balloon was deflated and withdrawn from the pig. The animals were then examined bronchoscopically and tissues samples were taken for pathology and quantification of drug uptake after 3 days, 31 days, 3 months, 6 months, 9 months and 12 months.

[0258] Example 13

[0259] The uncoated stent delivery catheters were inserted into the vascular lumen in pigs. The balloon was dilated, the stent was deployed and the deflated balloon was then withdrawn. The pharmaceutical formulation 1-15 of example 1 (10 -100 ml) is injected (about 5-15 mg drug per pig) at the site of stent implantation. The drug is then absorbed by injuried tissue. The animals are then examined and tissues samples are taken for pathology.

[0260] Example 14

[0261] The diseased tissue (breast cancer or atheroma or stenosis) was removed surgically from a human body. The pharmaceutical formulation 1-15 of example 1 (10-100 ml) was then injected into or onto the surgical cavities created by the surgical intervention (about 5 – 20 mg drug). The local drug delivery includes injection by long needle, guide catheters, introducer sheath, drug infusion tube and other drug delivery catheters. The drug was then absorbed by tissue at the target site.

[0262] Example 15

[0263] 6 PTCA balloon catheters (3.5 and 3.0 mm in diameter and 20 mm in length) were inflated at 1-3 atm. The inflated balloon was loaded with a formulation 18-27 in example 1. The sufficient amount of drug on the balloon (3 microgram per square mm) was obtained. The inflated balloon was folded, and then dried. The coated folded balloon was then rewrapped and sterilized for animal testing.

[0264] The coated PTCA balloon catheter was inserted into target site in the blood vessels (LAD, LCX and RCA) in the 25-45 ib pig was inflated to 12 atm. The stretch ratio (the ratio of balloon diameter to vessel diameter) was about 1.15 -1.20. The drug was delivered into the target tissue in 30-60 seconds. The balloon catheter was then deflated and was withdrawn from the animal body. The target blood vessel was harvested at 0.25 -24 hours after inflation. The drug content in the target tissue and the residual drug remained on the balloon were analyzed by tissue extraction and HPLC. In some of the animal tests the stent was crimped on the drug coated balloon catheters prior to deployment. In chronic animal tests,

angiography was performed before and after all interventions and at 28-35 days after the procedure. Luminal diameters were measured and late lumen loss was calculated. Late lumen loss is the difference between the minimal lumen diameter measured after the intervention and minimal lumen diameter after a period of follow-up time. Restenosis may be quantified by the diameter stenosis, which is the difference between the mean lumen diameters at follow-up and immediately after the procedure divided by the mean lumen diameter immediately after the procedure.

[0265] The animal test results for the Formulation 18-28 are reported here. All data is the average of five or six experimental data points.

[0266] The drug content of the formulation 18 on the 3.5 mm balloon catheters was 3.26 $\mu g/mm^2$. After the 15-30 minute procedure, the residual drug on the balloon was 15.92 μg or 2.3% of the total drug loading. The drug content in the tissue harvested 15-30 minutes after the procedure was 64.79 μg or 9.2% of the total drug content originally loaded on the balloon. If the 18 mm stent was depolyed by the coated balloon, the residual drug on the balloon was 31.96 μg or 4.5% of the total drug load, and the drug content in tissue harvested 15-30 minutes after the procedure was 96.49 μg, or 13.7% of drug load. The stretch ratio was 1.3 in the procedure. The late lumen loss after 28-35 days was 0.10 (sd 0.2) mm. . The diameter stenosis was 3.3%.

[0267] The drug content of the formulation 19 on the 3.5 mm balloon catheters was 3.08 $\mu g/mm^2$. After the 15-30 minute procedure, the residual drug on the balloon was 80.58 μg or 11.4% of the total drug load. The drug content in tissue harvested 15-30 minutes after the procedure was 42.23 μg or6.0% of the total drug load. After 28-35 days late lumen loss was 0.30 (sd 0.23) mm. The diameter stenosis was 5.4%.

[0268] The drug content of formulation 20 on the 3.5 mm balloon catheters was 3.61 $\mu g/mm^2$. After the 15-30 minute procedure, the residual drug on the balloon was 174.24 μg or 24.7% of the total drug load. The drug content in tissue harvested 15-30 minutes after the procedure was 83.83 μg or 11.9% of the total drug load. When deployed with a pre-crimped 18 mm stent, the residual drug on the balloon was 114.53 μg or 16.1% of the total drug load, and the drug content in the tissue harvested 15-30 minutes post procedure was 147.95 μg or 18.1% of the total

drug load. The stretch ratio was 1.3 in the procedure. Late lumen loss after 28-35 days was 0.10 (sd 0.1) mm. The diameter stenosis was 3.4%.

[0269] The drug content of formulation 21 on the 3.5 mm balloon catheters was 4.71 $\mu g/mm^2$. After the 15-30 minute procedure, the residual drug on the balloon was 44.39 μg or 6.3% of the total drug load. The drug content in tissue harvested 15-30 minutes after the procedure was 77.87 μg or 11.0% of the total drug load. After 28-35 days minimal lumen diameter was 0.23 (sd 0.44) mm. The diameter stenosis was 7.3%.

[0270] The drug content of formulation 22 on the 3.5 mm balloon catheters was 3.85 $\mu g/mm^2$. After the 15-30 minute procedure, the residual drug on the balloon was 24.59 μg or 3.5% of the total drug load. The drug content in tissue harvested 15-30 minutes after the procedure was 37.97 μg or 5.4% of the total drug load. After 28-35 days late lumen loss was 0.33 (sd 0.14) mm. The diameter stenosis was 6.7%.

[0271] The drug content of formulation 23 on the 3.5 mm balloon catheters was 3.75 $\mu g/mm^2$. After 60 minute procedure, the residual drug on the balloon was 0.82 μg or 0.1 % of the total drug load. The drug content in the tissue harvested 60 minutes after the procedure was 45.23 μg or 5.5% of the total drug load. After 28-35 days late lumen loss was 0.49 (sd 0.26) mm. The diameter stenosis was 11.3%.

[0272] The drug content of formulation 24 on the 3.5 mm balloon catheters was 3.35 $\mu g/mm^2$. After the 60 minute procedure, the residual drug on the balloon is 62.07 μg and 7.5% of the total drug loading. The drug content in the tissue harvested 60 minutes after the procedure was 40.55 μg or 4.9% of the total drug load. After 28-35 days late lumen loss was 0.47 (sd 0.33) mm. The diameter stenosis was 9.9%.

[0273] The drug content of formulation 25 on the 3.5 mm balloon catheters was 3.41 $\mu g/mm^2$. After the 60 minute procedure, the residual drug on the balloon was 50.0 μg or 6.0% of the total drug load. The drug content in the tissue harvested 60 mnutes post procedure was 26.72 μg or 3.2% of the total drug load. After 28-35 days late lumen loss was 0.36 (sd 0.41) mm. The diameter stenosis was 9.3%.

[0274] The drug content of formulation 28 on the 3.5 mm balloon catheters was 3.10 μg/mm^2. After the procedure, the residual drug on the balloon was 1.9% of the total drug load. The drug content in tissue harvested 2 hours after the procedure was 34.17 μg or 5.0% of the total drug load. In tissue harvested after the procedure, the drug content in tissue was 28.92 μg or 4.2% of the total drug load.

[0275] The drug content of control formulation (uncoated balloon) on the 3.5 mm balloon catheters was 0.0 μg/mm^2. After the procedure, residual drug on the balloon was 0% of the total drug load. The drug content in tissue harvested 15 minutes after the procedure was 0 μg. In tissue harvested 24 hours after the procedure, the drug content in tissue was 0 μg. after 28-35 days late lumen loss was 0.67 (sd 0.27) mm. The diameter stenosis is 20.8%. In the second repeat experiment, the stretch ratio was 1.3. The late lumen loss was 1.1 (sd 0.1). The diameter stenosis was 37.5%.

[0276] The drug content of formulation 26 on the 3.5 mm balloon catheters was 3.21 μg/mm^2. After the 15-30 minute procedure, the residual drug on the balloon was 13.52 μg or 1.9% of the total drug loading. The drug content in the tissue was 28.32 μg or 4.0% of the total drug load. When the balloon was deployed with a pre-crimped 18 mm stent, the residual drug on the balloon was 26.45 μg or 3.7% of the total drug load. The drug content in tissue was 113.79 μg or 16.1% of the total drug load. After 28-35 days, late lumen loss was 0.27 (sd 0.15) mm. The diameter stenosis was 7.1%.

[0277] The drug content of formulation 27 without additive on the 3.5 mm balloon catheters was 4.22 μg/mm^2. After the 15-30 minute procedure, the residual drug on the balloon was 321.97 μg or 45.6% of the total drug load. The drug content in the tissue was 12.83 μg or 1.8% of the total drug load.

[0278] The drug absorption of the formulation 18-25 in the invention is higher than those of formulation 26 and formulation 27. Late lumen loss after 28-35 days follow up was improved.

[0279] Example 16

[0280] 6 PTCA balloon catheters (3.5 and 3.0 mm in diameter and 20 mm in length) were inflated at 1-3 atm. The inflated balloon was loaded with a formulation

18-25 in example 1. The sufficient amount of drug on the balloon (3 μg/mm^2) was obtained. The inflated balloon was dried. The drug coated balloon was then loaded with a top coating formulation. The top coating formulation in acetone or ethanol was chosen from gentisic acid, methyl paraben, acetic acid, Tween 80, Tween 20, vanillin and aspirin. The coated folded balloon was dried, then rewrapped and sterilized for animal testing.

[0281] A floating experiment was designed to test how much drug is lost during balloon catheter insertion and transit to the target site prior to inflation. A control balloon catheter was coated with formulation 18. Top-coated catheters also were prepared having a top coating of propyl paraben. For top-coated catheters, the balloon catheter was coated with formulation 18, then dried, 25-50 mg propyl paraben (about 50% of paclitaxel by weight) in acetone was coated over the formulation 18 coating. Each of the control and top-coated balloon catheters was inserted in pig arteries. The floating time in pig arterial vasculature was 1 minute. The drug, additive and top coating were released. The catheter was then withdrawn. The residual drug on the balloon catheters was analyzed by HPLC. The residual drug content of the control balloon catheters was 53% of the total drug loading. The residual drug content of the top-coated balloon catheter was 88%. The top coat reduced drug loss in the vasculature during conditions that simulate transit of the device to a site of therapeutic intervention. The same animal tests were performed as in Example 15 with formulation 18 first coated on the balloon, and propyl paraben as a top coating layer overlying the first coating layer. The drug content on the 3.5 mm balloon catheter was 3.39 μg/mm^2. After the procedure, residual drug on the balloon was 64.5 μg, or 8.6% of the total drug load. The drug content in the tissue was 28.42 μg, or 4% of the total drug load.

[0282] Example 17

[0283] 6 PTCA balloon components (3.5 and 3.0 mm in diameter and 20 mm in length) were loaded with formulation 18 provided in Example 1. A sufficient amount of drug (3 μg/mm^2) was obtained on the balloon surface. The balloon was dried.

[0284] A formulation for a top coating layer was then prepared. The formulation of the top coating layer was paclitaxel, and one additive chosen from

Tween 20, Tween 80, polypropylene glycol-425 (PPG-425), and polypropyl glycol-1000 (PPG-1000), in acetone. The balloon surface of the control catheters was only loaded with formulation 18. 25-50 mg of the top coating formulation (about 50% of paclitaxel by weight) in acetone was coated over the formulation 18 coating layer on the other balloon surfaces. The coated balloons were dried for drug releasing testing in vitro.

[0285] The releasing experiment was designed to test how much drug is lost during balloon inflation. Each of the coated balloons were inflated to 12 atm. in 1% BSA solution at 37°C for 2 minutes. The drug, additive and top coating were released. The residual drug on the balloon catheters was analyzed by HPLC. The residual drug content of the control balloon catheter was 34% of the total drug loading. The residual drug content of of the ballon catheter that included a top coating layer with Tween 20, Tween 80, polypropylene glycol-425 (PPG-425) or polypropyl glycol-1000 (PPG-1000) was 47%, 56%, 71% and 81%, respectively. Thus, the top coating layer reduced drug loss in the tests in vitro during inflation of the balloon components.

WHAT IS CLAIMED IS:

1. A method for treating a respiratory disorder in a mammal comprising:

administering a pharmaceutical formulation comprising an effective amount of a drug and an additive to said mammal orally, parenterally, intravascularly, intranasally, intrabronchially, transdermally, rectally, or via an impregnated vascular stent or balloon catheter into a body passage, wherein said drug is chosen from rapamycin and analogues thereof and paclitaxel and analogues thereof.

2. The method according to claim 1, wherein said administering comprises delivery via a mist route chosen from aerosol inhalation, dry powder inhalation, liquid inhalation, and liquid instillation.

3. The method according to claim 2, wherein the mist is produced by either a nebulizer, a hand-held meter dose inhaler (MDI), or dry powder (DPI) inhaler.

4. The method according to claim 1, wherein the respiratory disorder is chosen from chronic bronchitis, cystic fibrosis, interstitial fibrosis, nasal and sinus dysplasia, bronchopulmonary dysplasia and neoplasia, and emphysema.

5. The method according to claim 1, wherein the additive enhances absorption of the drug into tissue of the body passage of the respiratory and sinus system.

6. The method according to claim 1, wherein the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions.

7. The method according to claim 1, wherein the additive is at least one of a surfactant and a chemical compound.

8. The method according to claim 7, wherein the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone,

hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

9. The method according to claim 7, wherein the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof.

10. The method according to claim 7, wherein the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups.

11. The method according to claim 10, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

12. The method according to claim 1, wherein the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside,

n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

13. The method according to claim 7, wherein the surfactant is chosen from PEG-fatty acids and PEG-fatty acid mono and diesters, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglyceryl fatty acids, propylene glycol fatty acid esters, sterols and derivatives thereof, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, and sorbitan fatty acid esters.

14. The method according to claim 7, wherein the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil, PEG-8 caprylic /capric glycerides, and PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-

maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, edrophonium chloride, domiphen bromide, dialkylesters of sodium sulfonsuccinic acid, sodium dioctyl sulfosuccinate, sodium cholate, sodium taurocholate, and derivatives thereof.

15. The method according to claim 10, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine (Aminoacids); acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid (organic acids and anhydrides); cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U (vitamins); albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin,

catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols, and derivatives thereof.

16. The method according to claim 1, wherein the pharmaceutical formulation further comprises an additional drug.

17. The method according to claim 16, wherein the additional drug is chosen from corticosteroids, anticholinergics, beta-agonists, non-steroidal anti-inflammatory drugs, macrolide antibiotics, bronchodilators, leukotriene receptor inhibitors, cromolyn sulfate, and combinations thereof.

18. A pharmaceutical formulation comprising an effective amount of a drug for treatment of a respiratory or sinus system, and an additive that enhances absorption of the drug into tissue of the respiratory system, and wherein the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions.

19. The formulation according to claim 18, wherein the formulation is an aqueous aerosol formulation, a dry powder aerosol formulation, or a propellant-based formulation.

20. The formulation according to claim 18, wherein the drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof.

21. The formulation according to claim 18, wherein the drug is present in a concentration of about 0.05 mg/ml to about 600 mg/ml.

22. The formulation according to claim 18, wherein the additive is at least one of a surfactant and a chemical compound.

23. The formulation according to claim 22, wherein the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

24. The formulation according to claim 22, wherein the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof.

25. The formulation according to claim 22, wherein the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups.

26. The formulation according to claim 25, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

27. The formulation according to claim 18, wherein the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG

oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl

paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

28. The formulation according to claim 22, wherein the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate,, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil,, PEG-8 caprylic /capric glycerides, PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-3 oleyl ether and PEG-4 lauryl ether, sucrose monopalmitate, sucrose

monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid (ionic surfactants), n-octyl- β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, and their derivatives.

29. The formulation according to claim 25, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid ; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-

glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine above described, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, and acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols and a mixture of the additives, and their derivatives.

30. The formulation according to claim 18, wherein the drug is present in a concentration of about 0.05 mg/g to about 990 mg/g.

31. The formulation according to claim 18, wherein the formulation further comprises an additional drug.

32. The formulation according to claim 31, wherein the additional drug is chosen from corticosteroids, anticholinergics, beta-agonists, non-steroidal anti-inflammatory drugs, macrolide antibiotics, bronchodilators, leukotriene receptor inhibitors, cromolyn sulfate, and combinations thereof.

33. A method for treating a respiratory system in a mammal comprising:

(1) forming an aerosol of a dispersion of particles, wherein the particles comprise a water insoluble drug and an additive that enhances absorption of the drug into tissue of the respiratory system; and

(2) administering the aerosol to the respiratory system of the mammal.

34. The method according to claim 33, wherein the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions.

35. The method according to claim 34, wherein the additive is at least one of a surfactant and a chemical compound.

36. The method according to claim 35, wherein the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

37. The method according to claim 35, wherein the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof.

38. The method according to claim 35, wherein the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups.

39. The method according to claim 38, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

40. The method according to claim 33, wherein the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone,

ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

41. The method according to claim 35, wherein the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil, PEG-8 caprylic /capric glycerides, PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol

ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-3 oleyl ether and PEG-4 lauryl ether, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid (ionic surfactants), n-octyl- β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, and their derivatives.

42. The method according to claim 38, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid ; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins,

lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine above described, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols and a mixture of the additives, and their derivatives.

43. The method according to claim 33, wherein the water insoluble drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof.

44. An aerosol device for delivering a drug to a respiratory system, the device comprising a pharmaceutical formulation comprising a water insoluble drug and an additive, wherein the additive enhances absorption of the drug into tissue of the respiratory system.

45. The device according to claim 44, wherein the pharmaceutical formulation is an aqueous, propellant based, or dry powder formulation.

46. The device according to claim 44, wherein the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions.

47. The device according to claim 46, wherein the additive is at least one of a surfactant and a chemical compound.

48. The device according to claim 47, wherein the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

49. The device according to claim 47, wherein the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof.

50. The device according to claim 47, wherein the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups.

51. The device according to claim 50, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

52. The device according to claim 44, wherein the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol,

benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

53. The device according to claim 47, wherein the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate,, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil,, PEG-8 caprylic /capric glycerides, PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate, polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan

monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-3 oleyl ether and PEG-4 lauryl ether, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid (ionic surfactants), n-octyl- β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, and their derivatives.

54. The device according to claim 50, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid ; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt,

tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine above described, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols and a mixture of the additives, and their derivatives.

55. The device according to claim 44, wherein the water insoluble drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof.

56. The device according to claim 44, wherein the aerosol device is one of a nebulizer, a hand-held meter dose inhaler, or a dry powder inhaler.

57. A device sized and configured for insertion into a passage of a respiratory system, the device comprising a layer overlying an exterior surface of the device, the layer comprising a water insoluble drug for the treatment of the respiratory system and an additive that enhances absorption of the drug into tissue of the respiratory system.

58. The device according to claim 57, wherein the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one

of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions.

59. The device according to claim 57, wherein the device is a balloon catheter or a stent.

60. The device according to claim 57, wherein the water insoluble drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof.

61. The device according to claim 58, wherein the additive is at least one of a surfactant and a chemical compound.

62. The device according to claim 61, wherein the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

63. The device according to claim 61, wherein the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof.

64. The device according to claim 61, wherein the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups.

65. The device according to claim 64, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl

ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

66. The device according to claim 57, wherein the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic

acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

67. The device according to claim 61, wherein the surfactant is chosen from esters of lauric acid, oleic acid, and stearic acid, PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate, PEG-20 oleate, PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-25 trioleate, PEG-60 corn glycerides, PEG-60 almond oil, PEG-40 palm kernel oil, PEG-8 caprylic /capric glycerides, PEG-6 caprylic /capric glycerides, PEG-6 corn oil, PEG-6 almond oil, PEG-6 apricot kernel oil, PEG-6 olive oil , PEG-6 peanut oil, PEG-6 hydrogenated palm kernel oil, PEG-6 palm kernel oil , PEG-6 triolein, PEG-8 corn oil, PEG-20 corn glycerides, PEG-20 almond glycerides, polyglyceryl oleate, polyglyceryl-2 dioleate, polyglyceryl-10 trioleate, polyglyceryl stearate, polyglyceryl laurate, polyglyceryl myristate, polyglyceryl palmitate, and polyglyceryl linoleate, polyglyceryl-10 laurate, polyglyceryl-10 oleate, polyglyceryl-10 mono, dioleate, polyglyceryl-10 stearate, polyglyceryl-10 laurate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate,

polyglyceryl-10 linoleate, polyglyceryl-6 stearate, polyglyceryl-6 laurate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, and polyglyceryl-6 linoleate, and polyglyceryl polyricinoleate, propylene glycol monolaurate, propylene glycol ricinoleate, propylene glycol monooleate, propylene glycol dicaprylate/dicaprate, propylene glycol dioctanoate, PEG-20 sorbitan monolaurate, PEG-20 sorbitan monopalmitate, PEG-20 sorbitan monostearate, PEG-20 sorbitan monooleate, PEG-3 oleyl ether and PEG-4 lauryl ether, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucop- yranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside, PEG-10-100 nonyl phenol, PEG-15-100 octyl phenol ether, Tyloxapol, octoxynol, nonoxynol, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid (ionic surfactants), n-octyl- β -D-glucopyranoside, octoxynol-9, Polysorbates, Tyloxapol, octoxynol, nonoxynol, isononylphenylpolyglycidol, PEG glyceryl monooleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate, polyglyceryl-10 oleate, polyglyceryl-10 laurate, polyglyceryl-10 palmitate, polyglyceryl-10 stearate, and their derivatives.

68. The device according to claim 64, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid ; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol

diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid, glucomic acid, gluconolactone, D-glucoheptono-1,4-lactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, erythronic acid lactone, ribonic acid lactone, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and amine above described, lysine/glutamic acid, lysine acetate, lactobionic acid/meglumine, lactobionic acid/tromethanemine, lactobionic acid/diethanolamine, lactic acid/meglumine, lactic acid/tromethanemine, lactic acid/diethanolamine, gentisic acid/meglumine, gentisic acid/tromethanemine, gensitic acid/diethanolamine, vanillic acid/meglumine, vanillic acid/tromethanemine, vanillic acid/diethanolamine, benzoic acid/meglumine, benzoic acid/tromethanemine, benzoic acid/diethanolamine, acetic acid/meglumine, acetic acid/tromethanemine, acetic acid/diethanolamine, polyglycidol, glycerols, multiglycerols and a mixture of the additives, and their derivatives.

69. A method for treating a respiratory system comprising:

inserting a balloon catheter comprising a coating layer into an airway, wherein the coating layer comprises a drug and an additive;

inflating the balloon catheter and releasing the drug to a wall of the airway;

deflating the balloon; and

withdrawing the balloon catheter from the airway.

70. The method according to claim 69, wherein the additive enhances absorption of the drug into tissue of the respiratory or sinus system.

71. The method according to claim 69, wherein the additive comprises a hydrophilic part and a drug affinity part, wherein the drug affinity part is at least one of a hydrophobic part, a part that has an affinity to the therapeutic agent by hydrogen bonding, and a part that has an affinity to the therapeutic agent by van der Waals interactions.

72. The method according to claim 69, wherein the drug is chosen from paclitaxel and analogues thereof and rapamycin and analogues thereof.

73. The method according to claim 71, wherein the additive is at least one of a surfactant and a chemical compound.

74. The method according to claim 73, wherein the chemical compound is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol, phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

75. The method according to claim 73, wherein the surfactant is chosen from ionic, nonionic, aliphatic, and aromatic surfactants, PEG fatty esters, PEG omega-3 fatty esters, ether, and alcohols, glycerol fatty esters, sorbitan fatty esters, PEG glyceryl fatty esters, PEG sorbitan fatty esters, sugar fatty esters, PEG sugar esters, and derivatives thereof.

76. The method according to claim 73, wherein the chemical compound has one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups.

77. The method according to claim 76, wherein the chemical compound having one or more hydroxyl, amino, carbonyl, carboxyl, acid, amide or ester groups is chosen from amino alcohols, hydroxyl carboxylic acid, ester, anhydrides, hydroxyl ketone, hydroxyl lactone, hydroxyl ester, sugar phosphate, sugar sulfate, ethyl oxide, ethyl glycols, amino acids, peptides, proteins, sorbitan, glycerol, polyalcohol,

phosphates, sulfates, organic acids, esters, salts, vitamins, combinations of amino alcohol and organic acid, and their substituted molecules.

78. The method according to claim 69, wherein the additive is chosen from p-isononylphenoxypolyglycidol, PEG laurate, Tween 20, Tween 40, Tween 60, PEG oleate, PEG stearate, PEG glyceryl laurate, PEG glyceryl oleate, PEG glyceryl stearate, polyglyceryl laurate, plyglyceryl oleate, polyglyceryl myristate, polyglyceryl palmitate, polyglyceryl-6 laurate, plyglyceryl-6 oleate, polyglyceryl-6 myristate, polyglyceryl-6 palmitate, polyglyceryl-10 laurate, plyglyceryl-10 oleate, polyglyceryl-10 myristate, polyglyceryl-10 palmitate PEG sorbitan monolaurate, PEG sorbitan monolaurate, PEG sorbitan monooleate, PEG sorbitan stearate, PEG oleyl ether, PEG laurayl ether, octoxynol, monoxynol, tyloxapol, sucrose monopalmitate, sucrose monolaurate, decanoyl-N-methylglucamide, n-decyl - β -D-glucopyranoside, n-decyl - β -D-maltopyranoside, n-dodecyl - β -D-glucopyranoside, n-dodecyl - β -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- β -D-glucopyranoside, n-heptyl - β -D-thioglucoside, n-hexyl - β -D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl - β -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- β -D-glucopyranoside, octyl - β -D-thioglucopyranoside; cystine, tyrosine, tryptophan, leucine, isoleucine, phenylalanine, asparagine, aspartic acid, glutamic acid, and methionine; acetic anhydride, benzoic anhydride, ascorbic acid, 2-pyrrolidone-5-carboxylic acid, sodium pyrrolidone carboxylate, ethylenediaminetetraacetic dianhydride, maleic and anhydride, succinic anhydride, diglycolic anhydride, glutaric anhydride, acetiamine, benfotiamine, pantothenic acid; cetotiamine; cycothiamine, dexpanthenol, niacinamide, nicotinic acid, pyridoxal 5-phosphate, nicotinamide ascorbate, riboflavin, riboflavin phosphate, thiamine, folic acid, menadiol diphosphate, menadione sodium bisulfite, menadoxime, vitamin B12, vitamin K5, vitamin K6, vitamin K6, and vitamin U; albumin, immunoglobulins, caseins, hemoglobins, lysozymes, immunoglobins, a-2-macroglobulin, fibronectins, vitronectins, firbinogens, lipases, benzalkonium chloride, benzethonium chloride, docecyl trimethyl ammonium bromide, sodium docecylsulfates, dialkyl methylbenzyl ammonium chloride, and dialkylesters of sodium sulfonsuccinic acid, L-ascorbic acid and its salt, D-glucoascorbic acid and its salt, tromethamine, triethanolamine, diethanolamine, meglumine, glucamine, amine alcohols, glucoheptonic acid,

glucomic acid, hydroxyl ketone, hydroxyl lactone, gluconolactone, glucoheptonolactone, glucooctanoic lactone, gulonic acid lactone, mannoic lactone, ribonic acid lactone, lactobionic acid, glucosamine, glutamic acid, benzyl alcohol, benzoic acid, hydroxybenzoic acid, propyl 4-hydroxybenzoate, lysine acetate salt, gentisic acid, lactobionic acid, lactitol, sinapic acid, vanillic acid, vanillin, methyl paraben, propyl paraben, sorbitol, xylitol, cyclodextrin, (2-hydroxypropyl)-cyclodextrin, acetaminophen, ibuprofen, retinoic acid, lysine acetate, gentisic acid, catechin, catechin gallate, tiletamine, ketamine, propofol, lactic acids, acetic acid, salts of any organic acid and organic amine, polyglycidol, glycerol, multiglycerols, galactitol, di(ethylene glycol), tri(ethylene glycol), tetra(ethylene glycol), penta(ethylene glycol), poly(ethylene glycol) oligomers, di(propylene glycol), tri(propylene glycol), tetra(propylene glycol, and penta(propylene glycol), poly(propylene glycol) oligomers, a block copolymer of polyethylene glycol and polypropylene glycol, and derivatives and combinations thereof.

79. The method according to claim 69, wherein the drug can be released to the wall of the airway prior to, during, or after an asthma attack.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/007177

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L29/16 A61K9/12 A61K31/337 A61K31/436
ADD. A61P11/06

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)
A61L A61K

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 practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/183380 A1 (HUNTER WILLIAM L [CA]) 5 December 2002 (2002-12-05) paragraph [0205] - paragraph [0212] paragraph [0164] - paragraph [0171]	1-17
X	WO 97/25977 A (NOVARTIS AG [CH]; TIEMESSEN HARRY [DE]) 24 July 1997 (1997-07-24) page 13, last paragraph page 14, paragraph 2	1-17

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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
2 September 2008	02/12/2008

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/007177

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHHAJED PRASHANT N ET AL: "Patterns of pulmonary complications associated with sirolimus." RESPIRATION; INTERNATIONAL REVIEW OF THORACIC DISEASES 2006, vol. 73, no. 3, March 2006 (2006-03), pages 367-374, XP002489455 ISSN: 0025-7931 abstract * p. 368-372 : Case reports *	1-17
Y	CHAMPION LAURE ET AL: "Brief communication: sirolimus-associated pneumonitis: 24 cases in renal transplant recipients." ANNALS OF INTERNAL MEDICINE 4 APR 2006, vol. 144, no. 7, 4 April 2006 (2006-04-04), pages 505-509, XP002489456 ISSN: 1539-3704 abstract; table 1	1-17
Y	OSTOROS ET AL: "26 Paclitaxel induced pulmonary fibrosis" LUNG CANCER, ELSEVIER, AMSTERDAM, NL, vol. 41, 1 August 2003 (2003-08-01), page S280, XP005875969 ISSN: 0169-5002 abstract	1-17
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Y	WO 2007/047416 A (ABBOTT LAB [US]; BURKE SANDRA E [US]; CROMACK KEITH R [US]; MACK MATTH) 26 April 2007 (2007-04-26) paragraph [0136] - paragraph [0138]	1-17
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/007177

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-17

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17

   Method for treating at least one of asthma, COPD and chronic sinusitis, comprising administering .... a drug ..... chosen from rapamycin ...: and paclitaxel.

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2. claims: 18-32

   A pharmaceutical composition comprising ... a drug for treatment of a respiratory or sinus system and an additive.

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3. claims: 33-43

   A method for treating a respiratory system ... comprising (1) forming an aerosol of ... a water insoluble drug and an additive and (2) administering the aerosol.

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4. claims: 44-56

   An aerosol device ... comprising a pharmaceutical formulation comprising a water insoluble drug and an additive.

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5. claims: 57-68

   A device ... comprising a water insoluble drug for the treatment of the respiratory system and an additive.

   ---

6. claims: 69-79

   A method for treating a respiratory system comprising inserting a balloon catheter comprising ... a drug and an additive.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/007177

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