air driven nebulizer system with an adequate air flow and equipped with a mouthpiece or suitable face mask. While rhDNAse/ PULMOZYNE®, and has been effective in improving the lung function, reducing rate of infection and improving the quality of life for Cystic Fibrosis patients, it has not been approved for other muco-obstructive disease. Doctors do utilize it for other diseases on a case-by-case basis.

PULMOZYNE®, has several limitations. PULMOZYNE®, has low deposition efficiency, reported in the range between 7.8% and 31.2%. PULMOZYNE®, also has storage restrictions, including the need to be stored in a protective foil pouch under refrigeration. A dose of PULMOZYNE®, takes 20-40 minutes to administer. Further, the nebulizer cup must be rinsed with warm water, cleaned of excess liquid, and allowed to air dry following each use. Further cleaning may be required, such as washing the nebulizer cup, mouthpiece, and/or mask with soap and/or disinfectant. Further, while the drug may be safe at these doses in ICU, it is not suitable for chronic out-patient use. Therefore, it has never been utilized and approved for chronic out-patient use.

The disadvantages of PULMOZYNE®, reduce effectiveness and patient adherence to the treatment, jeopardizing the rhDNAse therapy. This molecule has the propensity to readily form dimers and lose its mucolytic activity. Therefore, without stabilizing the activity and using an appropriate delivery method, only a fraction of the dose makes it to the lung. Furthermore, the particle size, flight characteristics, and delivery method have impact on the level of penetration of the drug into the airways and lungs.

Therefore, it is important to formulate and deliver the molecule in a way to stabilize the active form and ensure deeper penetration into the lungs and convenient delivery of a significant percentage, e.g., 60%, of the dose to patient airways.

There is also a desire to protect some mucolytic from degradation or loss of activity before being delivered to the treatment site. Certain mucolytic agents can readily oxidize before reaching their target, which may diminish their efficacy. This may explain inconsistent results in clinical trials. The need exists to provide protection from degradation or loss of activity for a mucolytic in order to maximize its potency.

SUMMARY

Accordingly, it is an object of the present disclosure to overcome these and other drawbacks of the prior art by providing novel inhalable therapeutic agents that allow effective dissolution of mucus.

In an aspect, there is provided a composition comprising a population of inhalable particles, wherein the particles comprise a first mucolytic contained in a biodegradable lipid encapsulation, and wherein the composition is for delivery via a dry powder inhaler, and the population of inhalable particles are sized to be from 0.01 μm to 49 μm, wherein the particle size is measured using laser diffraction whereby the population of inhalable particles are configured for predominant absorption at a target location of the airways of a subject,

wherein the target location of the airways of the subject is the upper respiratory tract or the lower respiratory tract;

wherein the first mucolytic is selected from a group of compounds consisting of: sodium 2-mercaptoethane sulfonate, N-acetylcysteine, bromhexine, ascorbic acid, di-peptide of glutamic acid, di-peptide of aspartic acid, Ambroxol Hydrochloride, DNAse, and a DNA cleaving agent;

wherein the particles further comprise an excipient selected from the group consisting of mannitol, magnesium stearate, sodium acetate, dipalmitoyl phosphatidylcholine (DPPC), soy lecithin, egg lecithin, cholesterol, DSPE (distearoyl-sn-glycero-phosphoethanolamine); DSPC (distearoylphosphatidylcholine); DOPC (dioleoylphosphatidylcholineDOPS (dioleoylphosphatidylserine); POPC (palmitoyloleoylphosphatidylcholine); DMPC (dimyristoyl phosphatidylcholine); DMPG (dimyristoyl phosphatidylglycerol); DSPG (distearoylphosphatidylglycerol); DEPC (dierucoylphosphatidylcholine); DOPE (dioleoly-sn-glycero-phophoethanolamine), and DPPG (1,2-Dipalmitoyl-sn-glycero-3-phosphorylglycerol sodium salt), and

wherein the composition comprises liposomes, microspheres, and engineered spray-dried particles.

In another aspect there is provided a method for preparing the composition as defined above, wherein the method comprises micronization, crystallization, freeze drying, spray freeze drying, or spray drying, wherein

(i) the spray drying inlet temperature is between 80 and 90°C;

(ii) the spray drying outlet temperature is between 55 and 65°C;

(iii) the spray drying feed rate is between 1 and 3 g/min; or

(iv) the spray drying pressure is between 3 and 5 bar.

In another aspect, there is provided the composition as defined above for use in therapy.

In another aspect, there is provided the use of the composition as defined above in the manufacture of a medicament for treatment of a muco-obstructive lung, sinus, ear, or airway disease, wherein the composition is to be delivered through the nose, mouth, trachea, or bronchia, and wherein the composition is to be delivered via nebulization or instillation.

It is another object of the present disclosure to provide novel inhalable therapeutic agents designed to provide effective treatment at lower doses of the drug so as to reduce possible side effects and allow for self-administration in repeated applications performed multiple times.

It is a further object of the present disclosure to provide novel inhalable therapeutic agents configured for administration either by a medical professional or self-administration so as to make such treatment suitable for out-patient delivery.

It is yet another object of the present disclosure to provide novel therapeutic agents configured to protect the active drug from degradation and prevent loss of mucolytic activity prior to its direct delivery at the target site of the airways, whereby preserving its potency until its immediate interaction at the target site. In the most basic form, the present disclosure may be described as at least one or several pluralities of inhalable particles. Each particle may include one or more mucolytic or another suitable active therapeutic agent contained within one or several different types of biodegradable encapsulations, desirably without the risk of pre-delivery interaction. The number and respective concentration of

CLAIMS

1. A composition comprising a population of inhalable particles, wherein the particles comprise a first mucolytic contained in a biodegradable lipid encapsulation, and wherein the composition is for delivery via a dry powder inhaler, and the population of inhalable particles are sized to be from 0.01 μm to 49 μm, wherein the particle size is measured using laser diffraction whereby the population of inhalable particles are configured for predominant absorption at a target location of the airways of a subject,

   wherein the target location of the airways of the subject is the upper respiratory tract or the lower respiratory tract;

   wherein the first mucolytic is selected from a group of compounds consisting of: sodium 2-mercaptoethane sulfonate, N-acetylcysteine, bromhexine, ascorbic acid, di-peptide of glutamic acid, di-peptide of aspartic acid, Ambroxol Hydrochloride, DNAse, and a DNA cleaving agent;

   wherein the particles further comprise an excipient selected from the group consisting of mannitol, magnesium stearate, sodium acetate, dipalmitoyl phosphatidylcholine (DPPC), soy lecithin, egg lecithin, cholesterol, DSPE (distearoyl-sn-glycero-phosphoethanolamine); DSPC (distearoylphosphatidylcholine); DOPC (dioleoylphosphatidylcholineDOPS (dioleoylphosphatidylserine); POPC (palmitoyloleoylphosphatidylcholine); DMPC (dimyristoyl phosphatidylcholine); DMPG (dimyristoyl phosphatidylglycerol); DSPG (distearoylphosphatidylglycerol); DEPC (dierucoylphosphatidylcholine); DOPE (dioleoly-sn-glycero-phophoethanolamine), and DPPG (1,2-Dipalmitoyl-sn-glycero-3-phosphorylglycerol sodium salt), and

   wherein the composition comprises liposomes, microspheres, and engineered spray-dried particles.

2. The composition of claim 1, wherein the first mucolytic is sodium 2-mercaptoethane sulfonate.

3. The composition of claim 1 wherein the first mucolytic is a DNAse.

4. The composition of claim 1, wherein the first mucolytic is a DNA cleaving agent.

5. The composition of claims 1 to 4 further comprising one or more short-acting beta-agonist, long-acting beta-agonist, short-acting muscarinic antagonist, long-acting muscarinic antagonist, immunosuppressant, antibiotic, antiviral, antifungal, corticosteroid, or additional anti-infective agent.

6. The composition of any one of claims 1 to 5, wherein the composition comprises an anti-infective agent selected from the group consisting of quinolone, nalidixic acid, ciprofloxacin, cinoxacin, sulfoamide, sulanilamide, sulfadiazine, sulfamethoxazole, sulfisoxazole, aminoglycoside, streptomycin, gentamicin, tobramycin, amikacin, netilmicin, Kanamycin,

tetracycline, chlortetracycline, oxytetracycline, methacycline, doxycycline, minocycline, para-aminobenzoic acid, diaminopyrimidine, trimethoprim, beta-lactam, penicillin, penicillin G benzathine, penicillin VK, ampicillin, amoxicillin, bacampicillin, carbenicillin, carbenicillin indanyl, ticarcillin, azlocillin, mezlocillin, piperacillin, penicillinase resistant penicillin, methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin, cephalosporin, first-generation cephalosporin, cefadroxil, cephalexin, cephradine, cephalothin, cephapirin, cefazolin, second-generation cephalosporin, cefaclor, cefamandole, cefonicid, cefoxitin, cefotetan, cefuroxime, aefuroxime axetil, cefinetazole, cefprozil, loracarbef, ceforanide, third-generation cephalosporin, cefepime, cefoperaZone, cefotaxime, ceftizoxime, ceftriaxone, ceftazidime, cefixime, cefpodoxime, ceftibuten, cefotaxime, imipenem, meropenem, aztreonam, clavulanic acid, sulbactam, tazobactam, beta-lactamase inhibitor, clavulanate, chloramphenicol, macrolide, erythromycin, azithromycin, clarithromycin, lincomycin, clindamycin, spectinomycin, polymyxin, polymyxin A, polymyxin B, polymyxin C, polymyxin D, polymyxin E, vancomycin, bacitracin, isoniazid, rifampin, ethambutol, ethionamide, aminosalicylic acid, cycloserine, capreomycin, sulfone, dapsone, sulfoxone sodium, clofazimine, and thalidomide.

7. The composition of any one of claims 1 to 6, wherein the composition comprises an antifungal agent selected from the group consisting of polyene, amphotericin B, nystatin, natamycin, flucytosine, imidazole, miconazole, clotrimazole, econazole, ketoconazole, triazole, itraconazole, fluconazole, griseofulvin, terconazole, butoconazole, ciclopirox, ciclopirox olamine, haloprogin, tolnaftate, naftifine, and terbinafine.

8. The composition of any one of claims 1 to 7, wherein the composition comprises a corticosteroid selected from the group consisting of flunisolide, fluticasone, fluocortolone, triamcinolone, beclomethasone, budesonide, mometasone, ciclesonide, prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone, and deflazacort.

9. The composition of any one of claims 1 to 8, wherein the composition comprises beta-agonist selected from the group consisting of bitolterol, fenoterol, isoprenaline, levosalbutamol, orciprenaline, pirbuterol, procaterol, ritodrine, salbutamol, terbutaline, albuterol, formoterol, bambuterol, clenbuterol, formoterol, salmeterol, indacaterol, olodaterol, and vilanterol.

10. The composition of any one of claims 1 to 9, wherein the composition comprises a long-acting muscarinic antagonist selected from the group consisting of aclidinium, glycopyrronium, glycopyrrolate, tiotropium, and umeclidinium.

11. The composition of any one of claims 1 to 10, wherein the composition comprises an antiviral agent selected from the group consisting of remdesivir, abacavir, adefovir, delavirdine, descovy, didanosine, doravirine, efavirenz, emtricitabine, entecavir, etravirine, lamivudine, loviride, nevirapine, rilpivirine, stavudine, tenofovir alafenamide, tenofovir disoproxil, zalcitabine, zidovudine, acyclovir, cidofovir, penciclovir, famciclovir, foscarnet, ganciclovir, valganciclovir, idoxuridine, ribavirin, taribavirin, sofosbuvir, telbivudine, trifluridine, valaciclovir, vidarabine, boceprevir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, simeprevir, telaprevir, tipranavir, bictegravir, elvitegravir, dolutegravir, raltegravir, oseltamivir, zanamivir, laninamivir, peramivir, ledipasvir, amprenavir,

amantadine, umifenovir, baloxavir marboxil, daclatasvir, docosanol, edoxudine, enfuvirtide, fomivirsen, ibacitabine, ibalizumab, letermovir, maraviroc, metisazone, moroxydine, nexavir, nitazoxanide, pleconaril, rimantadine, tromantadine, and vicriviroc.

12. The composition of any one of claims 1 to 11, wherein the first mucolytic, second mucolytic, short-acting beta-agonist, long-acting beta-agonist, short-acting muscarinic antagonist, long-acting muscarinic antagonist, immunosuppressant, antibiotic, antiviral, antifungal, corticosteroid, and/or additional anti-infective agent compound are:

(i) encapsulated in nanoparticles, microspheres, or liposomes;

(ii) engineered spray-dried particles.

13. The composition of any one of claims 1-12 wherein the inhalable particles are stored in a dry form.

14. The composition of any one of claims 1-13 wherein the inhalable particles are in a solution form.

15. The composition of any one of claims 1-12 wherein the particles comprise a first mucolytic contained in a biodegradable lipid encapsulation in a dry powder form that is to be administered via the dry powder inhaler.

16. The composition of claim 15, wherein the dry powder inhaler is configured upon activation to provide each dose of the composition containing from 5 miligrams to 200 milligrams of the first mucolytic.

17. A method for preparing the composition of any one of claims 1 to 12, wherein the method comprises micronization, crystallization, freeze drying, spray freeze drying, or spray drying, wherein

(i) the spray drying inlet temperature is between 80 and 90°C;

(ii) the spray drying outlet temperature is between 55 and 65°C;

(iii) the spray drying feed rate is between 1 and 3 g/min; or

(iv) the spray drying pressure is between 3 and 5 bar.

18. The composition of any one of claims 1 to 12 for use in therapy.

19. Use of the composition of any one of claims 1 to 12 in the manufacture of a medicament for treatment of a muco-obstructive lung, sinus, ear, or airway disease, wherein the composition is to be delivered through the nose, mouth, trachea, or bronchia, and wherein the composition is to be delivered via nebulization or instillation.

20. The use of claim 19, wherein the muco-obstructive lung, sinus, ear or airway disease is selected from the group consisting of primary ciliary dyskinesia, cystic fibrosis, sinusitis, rhinosinusitis, bronchiolitis obliterans, emphysema, bronchitis, bronchiectasis, pneumonitis, pneumonia, chronic obstructive pulmonary disease (COPD), chronic obstructive airway

disease (COAD), acute respiratory distress syndrome (ARDS), chronic respiratory distress syndrome (CRDS), or COVID-19.