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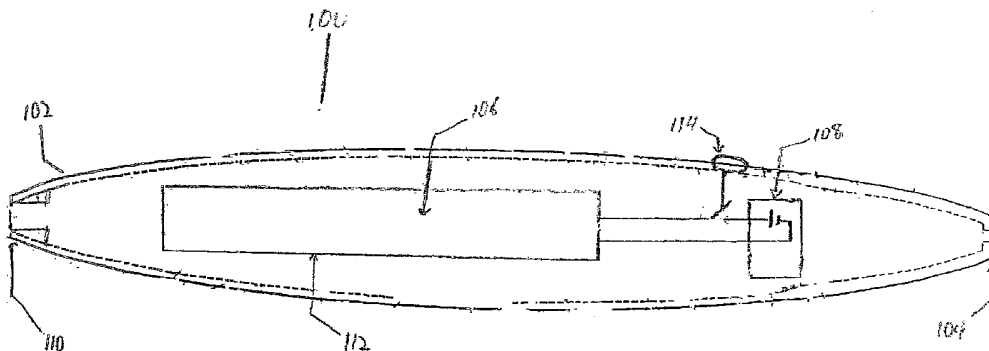
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(54) Title: DELIVERY OF DRUG AMINES THROUGH AN INHALATION ROUTE



(57) Abstract: The present invention relates to the delivery of drug amines through an inhalation route. Specifically, it relates to aerosols containing drug amines that are used in inhalation therapy. In one aspect of the present invention, a method of delivering an amine drug in an aerosol form is provided. The method comprises: a) heating a coating, which includes an amine drug salt on a substrate contained in a device to a temperature sufficient to volatilize the amine drug from the coating, b) by said heating, forming an amine drug vapor, and c) during said heating, drawing air through said device, condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound.



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DELIVERY OF DRUG AMINES THROUGH AN INHALATION ROUTE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. provisional application Ser. No. 60/380,819 entitled "Delivery of Drug Amines Through an Inhalation Route," filed May 13, 2002, Rabinowitz and Zaffaroni, the entire disclosure of which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to the delivery of drug amines through an inhalation route. Specifically, it relates to aerosols containing drug amines that are used in inhalation therapy.

BACKGROUND OF THE INVENTION

There are a number of compounds containing amines that are currently marketed as drugs. In certain circumstances, the presence of such functionality, however, can prevent effective drug delivery. This phenomenon could be due to a range of effects, including poor solubility and instability.

Inhaled drugs, however, have the potential to enter the systemic circulation and thereby circumvent a number of the problems associated with oral and other drug delivery methods. Moreover, by manipulation of particle size and/or density, delivery of drugs into the alveoli may be facilitated. Alveoli have a large surface area for drug absorption and are surrounded by an extensive capillary network which facilitates rapid passage of drugs into the pulmonary circulation. Furthermore, because blood returning from the lungs is pumped directly to the systemic arterial circulation, drugs inhaled into the alveoli have the potential to reach target organs very rapidly. Of particular importance is that drugs delivered in this manner reach their target site without being exposed to potentially degrading conditions in the gastrointestinal tract and without undergoing modification by first pass metabolism in the liver. Thus, it is desirable to provide a new route of administration for drug amines that rapidly produces peak plasma concentrations of the compounds. This invention provides a route of administration to accomplish this goal.

One type of inhalation aerosol is a condensation aerosol formed from vaporization of compounds. The use of vaporized drugs, thus, provides a method of maximizing alveolar delivery and rapidly delivering drugs to target organs. However, the heat required to vaporize a drug often also generates degradation products, which may decrease the efficacy of the thermal vapor and are undesirable to be delivered to the patient.

Particularly, the salt form of a drug is expected to lower a compound's vapor pressure, and consequently raise its vaporization temperature and potentially increase the amount of degradation product that is likely generated. Thus, a method that enhances drug volatilization without the formation of a substantial amount of degradation products with amine drug salts and a method for selected amine drug salts suitable for use in condensation aerosol is needed. Therefore, one object of the invention is to provide a thermal vapor of amine drug salts for inhalation therapy that does not contain a significant amount of thermal degradation products.

Furthermore, while many drugs may be delivered in their free base form using vaporization, such as those, for example, disclosed in U.S. Application No's: 10/150,591, 10/150,267, 10/155,705 and 10/152,640, some amine drugs are liquid in their free base form and thus, are not optimal in a vaporization method that uses films or coatings to generate the aerosol. In such cases, the physical or chemical stability of the coating may be enhanced through formation of the drug amine salt. Thus, another object of the present invention is to provide amine drugs with desirable properties for thermal vapor delivery.

While dry powder formulations and new liquid aerosol devices are being developed or are available for inhalation therapy. See for example, U.S. Pat. No. 5,993,805 to Sutton et al.; WO 0000176 to Robinson et al.; WO 9916419 to Tarara et al.; WO 0000215 to Bot et al.; U.S. Pat. No. 5,855,913 to Hanes et al.; and U.S. Pat. Nos. 6,136,295 and 5,874,064 to Edwards et al.; U.S. Pat. No. 6,131,570 to Schuster et al.; U.S. Pat. No. 5,724,957 to Rubsamen et al.; and U.S. Pat. No. 6,098,620 to Lloyd et al.; U.S. Pat. Nos. 5,586,550; 5,758,637; and 6,085,740 to Ivri et al.; and U.S. Pat. No. 5,938,117.

These technologies are limited, however. Dry powders require excipients to formulate the dry powders for appropriate delivery. Whereas with liquid aerosols, because the solubility of many drug compounds in water or other solvents suitable for liquid aerosol delivery is low, the total quantity of drug that can be delivered in a single breath is quite small. Thus, there is a need for condensation aerosol of amine drug salts that overcome these limitations. This invention provides such a means.

These and other features of the invention will be described in detail below. All publications, patents, and patent applications referred to herein are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

The present invention provides methods and reagents for selecting and generating novel amine drug condensation aerosols and vapors, as well as methods of delivering

amine drug aerosols, novel thermal vapor compositions, and methods for generating therapeutically effective inhalation doses of condensation aerosols.

In one aspect, the invention provides a method for selecting amine drugs salts for use in forming a condensation aerosol comprising:

- 5 a. dissolving or suspending a salt form of an amine drug in a solvent,
- b. coating the suspended or dissolved salt form of the amine drug on a substrate,
- c. heating the coated substrate to form a compound vapor,
- d. cooling the vapor to form aerosol particles,
- 10 e. collecting the aerosol particles,
- f. analyzing the collected particles to determine the purity of the aerosol particles; and
- g. selecting the amine drug based on a decomposition index less than 0.15.

Other preferred embodiments are those wherein the amine drug salt is selected from
15 the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, drugs for erectile dysfunction, drugs for migraine headache, drugs for the treatment of addiction, muscle relaxants, non-steroidal anti-inflammatory, opioid, or analgesics.

Amine drug salts selected by the above method can be used to form novel amine
20 drug condensations aerosols having preferably a mass median aerodynamic diameter between the range of 1 and 5, and less than 10% amine drug decomposition products. More preferable embodiments have a mass median aerodynamic diameter between the range of 1 and 3.

In another aspect of the invention, a method of delivering an amine drug in an
25 aerosol form is provided, comprising:

- a. heating a coating, which includes an amine drug salt on a substrate contained in a device to a temperature sufficient to volatilize the amine drug from the coating,
- b. by said heating, forming a amine drug vapor, and
- 30 c. during said heating, drawing air through said device, condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound.

In more preferred embodiments of the method, the coating of the amine drug salt used has a thickness between about 0.5 and 20 μm and the aerosol particles generated have a mass
35 median aerodynamic diameter between about 1 and 5 micrometers. More preferably, the

aerosol particles generated have a mass median aerodynamic diameter of about 1 to 3 micrometers with a geometric standard deviation of about 2.5 or less.

In a third aspect of the invention, novel thermal vapors are provided. These thermal vapors comprise gas and amine drug aerosol particles,

- 5 a. wherein said gas comprises an acid halide vapor, organic acid vapor, or organic acid decomposition product vapor, and
- b. wherein said amine drug aerosol particles
 - i. comprise at least 10 micrograms of an amine drug and less than 10% amine drug decomposition products relative to said total mass of amine drug
 - 10 in the particles, and
 - ii. have a mass median aerodynamic diameter in the range 1 to 5 micrometers.

These thermal vapors typically further contain a supersaturated amine drug vapor. Preferably such vapor is warmer than ambient temperature, and more preferably such

15 vapor is warmer than 100°C, 200°C, 250°C, or 300°C.

In yet another aspect of the invention, a method is provided for forming a therapeutically effective inhalation dose of drug amine aerosol particles with less than 10% degradation products, comprising:

- 20 a) providing a drug delivery article comprising a body defining an interior flow-through chamber having upstream and down stream chamber ends and a drug supply unit contained within such chamber, wherein said drug supply unit comprises a heat-conductive substrate coated with a composition comprising at least a therapeutic amount of amine drug salt having a decomposition index less than 0.10;
- b) heating said heat-conductive substrate to a temperature of greater than
- 25 200°C over a period of less than 5 seconds, thereby producing a vapor of a therapeutic dose of said amine drug salt; and
- c) flowing a gas through said chamber thereby cooling said vapor to form drug amine aerosol particles.

In the preferred embodiments, the thickness of the coating of amine drug salt on the

30 substrate is between about 0.2 and 20 μm . The typical amine drug particle mass median aerodynamic diameter of these embodiments is between about 1 and 5 micrometers. More preferably, the amine drug particle mass median aerodynamic diameter of these embodiments is between about 1 and 3 micrometers. In a more preferred embodiment the thermal vapor consists essentially of gas and amine drug aerosol particles.

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BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 is a side view showing internal details of a device for vaporizing a drug including an external chamber in accordance with the present invention for delivery of a drug to a mammal.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for screening amine drug salts for suitability in condensation aerosols; methods to deliver aerosols, novel vapor compositions, and methods to generate therapeutically effective amounts of amine aerosols. To facilitate understanding and the practice of the invention in its many and diverse applications, this description is organized as shown below.

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I. DEFINITIONS

II. CHARACTERISTICS OF THE AMINE DRUG SALTS

III. CHARACTERISTICS OF THE THERMAL VAPOR, AEROSOL AND/OR

15

PARTICLES

IV. METHODS

V. EXAMPLES

I. DEFINITIONS

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“Acid halide” refers to HF, HCl, HBr, HI, HAt.

“Aerodynamic diameter” of a given particle refers to the diameter of a spherical droplet with a density of 1 g/mL (the density of water) that has the same settling velocity as the given particle.

“Aerosol” refers to a suspension of solid or liquid particles in a gas.

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“Aerosol drug amine mass density” refers to the mass of drug amine per unit volume of aerosol.

“Aerosol mass density” refers to the mass of particulate matter per unit volume of aerosol.

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“Aerosol particle density” refers to the number of particles per unit volume of aerosol.

“Condensation aerosol” refers to an aerosol formed by vaporization of a substance followed by condensation of the substance into an aerosol.

“Decomposition index” refers to a number derived from an assay and described in Example 3 and 4. The number is determined by subtracting the fractional purity of the generated aerosol from 1.

35

“Drug” refers to any chemical compound that is used in the prevention, diagnosis, treatment, or cure of disease, for the relief of pain, or to control or improve any physiological or pathological disorder in humans or animals. Such compounds are oftentimes listed in the Physician’s Desk Reference (Medical Economics Company, Inc. at Montvale, NJ, 56th edition, 2002), which is herein incorporated by reference. The drugs are preferably other than recreational drugs. More specifically, the drugs are preferably other than recreational drugs used for non-medicinal recreational purposes, e.g., habitual use to solely alter one’s mood, affect, state of consciousness, or to affect a body function unnecessarily, for recreational purposes. Cocaine, amphetamine, methamphetamine, and their derivatives are recreational drugs specifically excluded from the term “drug”. The terms “drug” and “medication” are herein used interchangeably.

“Drug amine” refers to a drug containing a primary, secondary, or tertiary amine moiety and not a quaternary amine moiety.

“Drug amine” refers to a drug containing an amine moiety. Drug amine and “amine drug” are terms that mean the same and herein are used interchangeably.

“Drug amine salt” refers to a drug amine, where the amine group is protonated by an acid to form an ammonium salt with a corresponding counterion derived from the acid. The counterion is a pharmaceutically acceptable anion (e.g., Cl⁻ or CH₃CO₂⁻). The drug amines from which the salts are formed come from a variety of drug classes, including, without limitation, antibiotics, anticonvulsants, antidepressants, antiemetics, antihistamines, antiparkinsonian drugs, antipsychotics, anxiolytics, drugs for erectile dysfunction, drugs for migraine headaches, drugs for the treatment of alcoholism, drugs for the treatment of addiction, muscle relaxants, nonsteroidal anti-inflammatories, opioids, and other analgesics. Drug amine salt and “amine drug salt” are terms that mean the same and herein are used interchangeably.

Examples of antibiotics from which drug amine salts are formed include cephalexin; cephaloglycin; cephalosporins, such as cephalosporin C; cephadrine; amoxicillin; hetacillin; cyclacillin; and penicillins, such as penicillin N.

An example of anticonvulsants from which a drug amine salt is formed is tiagabine.

Examples of antidepressants from which drug amine salts are formed include amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dosulepin, doxepin, imipramine, lofepramine, medifoxamine, mianserin, mirtazapine, nortriptyline, protriptyline, trimipramine, viloxazine, citalopram, cotinine, duloxetine, fluoxetine, fluvoxamine, milnacipran, paroxetine, reboxetine, sertraline, tianeptine, iproniazid, isocarboxazid, moclobemide, phenylhydrazine, phenelzine, selegiline, sibutramine,

transylcypromine, ademetionine, amisulpride, amperozide, benactyzine, bupropion, idazoxan, metralindole, milnacipran, minaprine, nefazodone, nomifensine, ritanserin, roxindole, tofenacin, trazodone, tryptophan, and venlafaxine.

Examples of antiemetics from which drug amine salts are formed include
5 alizapride, azasetron, benzquinamide, bromopride, buclizine, chlorpromazine, cinnarizine, clebopride, cyclizine, diphenhydramine, diphenidol, dolasetron, droperidol, granisetron, hyoscine, metoclopramide, metopimazine, ondansetron, perphenazine, promethazine, prochlorperazine, scopolamine, triethylperazine, trifluoperazine, triflupromazine, trimethobenzamide, and tropisetron.

10 Examples of antihistamines from which drug amine salts are formed include azatadine, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexmedetomidine, diphenhydramine, doxylamine, hydroxyzine, cetirizine, fexofenadine, and promethazine.

Examples of antiparkinsonian drugs from which drug amine salts are formed include
15 amantadine, baclofen, biperiden, bztropine, orphenadrine, procyclidine, trihexyphenidyl, levodopa, carbidopa, selegiline, deprenyl, apomorphine, benserazide, bromocriptine, budipine, cabergoline, dihydroergokryptine, pramipexole, galanthamine, lazabemide, lisuride, memantine, mofegiline, pergolide, remacemide, and terguride.

Examples of antipsychotics from which drug amine salts are formed include
20 acetophenazine, alizapride, amperozide, benperidol, benzquinamide, bromperidol, butaperazine, carphenazine, carpipramine, chlorpromazine, chlorprothixene, clocapramine, clomacran, clopenthixol, clospirazine, clothiapine, cyamemazine, droperidol, flupenthixol, fluphenazine, fluspirilene, haloperidol, mesoridazine, metofenazate, molindone, penfluridol, pericyazine, perphenazine, pimozide, pipamerone, piperacetazine, pipotiazine,
25 prochlorperazine, promazine, remoxipride, sertindole, spiperone, sulpiride, thioridazine, thiothixene, trifluperidol, triflupromazine, trifluoperazine, ziprasidone, zotepine, zuclopenthixol, amisulpride, clozapine, melperone, olanzapine, quetiapine, and risperidone.

Examples of anxiolytics from which drug amine salts are formed include diazepam, alprazolam, triazolam, indiplon, zaleplon, mecloqualone, medetomidine, metomidate,
30 adinazolam, chlordiazepoxide, clobenzepam, flurazepam, lorazepam, midazolam, azacyclonol, buspirone, captodiamine, enciprazine, flesinoxan, ipsapirone, lesopitron, loxapine, methaqualone, propranolol, tandospirone, trazadone, zopiclone, and zolpidem.

Examples of drugs for erectile dysfunction from which amine salts are formed include cialis (IC351), sildenafil, vardenafil, apomorphine, apomorphine diacetate,
35 phentolamine, and yohimbine.

Examples of drugs for migraine headache from which drug amine salts are formed include almotriptan, eletriptan, alpiropride, codeine, dihydroergotamine, ergotamine, eletriptan, frovatriptan, isometheptene, lidocaine, lisuride, metoclopramide, naratriptan, oxycodone, propoxyphene, rizatriptan, sumatriptan, tolafenamic acid, zolmitriptan, 5 amitriptyline, atenolol, clonidine, cyproheptadine, diltiazem, doxepin, fluoxetine, lisinopril, methysergide, metoprolol, nadolol, nortriptyline, paroxetine, pizotifen, pizotyline, propanolol, protriptyline, sertraline, timolol, and verapamil.

Examples of drugs for the treatment of alcoholism from which drug amine salts are formed include naloxone and naltrexone.

10 An example of a drug for the treatment of addiction from which drug amine salts are formed is buprenorphine.

Examples of muscle relaxants from which drug amine salts are formed include baclofen, cyclobenzaprine, orphenadrine, quinine, and tizanidine.

15 Examples of nonsteroidal anti-inflammatories from which drug amine salts are formed include aceclofenac, alminoprofen, amfenac, bromfenac, carprofen, cinchophen, diclofenac, etodolac, mazipredone, meclofenamate, piroprofen, and tolafenamate.

20 Examples of opioids from which drug amine salts are formed include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, cipramadol, clonitazene, codeine, dextromoramide, dextropropoxyphene, diamorphine, dihydrocodeine, diphenoxylate, dipipanone, fentanyl, hydromorphone, lofentanil, levorphanol, meperidine, methadone, meptazinol, metopon, morphine, nalbuphine, nalorphine, oxycodone, papaveretum, pethidine, pentazocine, phenazocine, remifentanil, sufentanil, and tramadol.

25 Examples of other analgesics from which drug amine salts are formed include apazone, benzpiperylon, benzydramine, caffeine, clonixin, ethoheptazine, flupirtine, nefopam, orphenadrine, propacetamol, and propoxyphene.

Examples of acids used to form the drug amine salt include, without limitation, the following: hydrochloric acid; hydrobromic acid; formic acid; acetic acid; maleic acid; fumaric acid, benzoic acid, and trifluoroacetic acid.

30 “Drug amine degradation product” refers to a compound resulting from a chemical modification of the amine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

35 “Inhalable aerosol drug amine mass density” refers to the aerosol drug amine mass density produced by an inhalation device and delivered into a typical patient tidal volume.

“Inhalable aerosol mass density” refers to the aerosol mass density produced by an inhalation device and delivered into a typical patient tidal volume.

“Inhalable aerosol particle density” refers to the aerosol particle density of particles of size between 100 nm and 5 microns produced by an inhalation device and delivered into
5 a typical patient tidal volume.

“Mass median aerodynamic diameter” or “MMAD” of an aerosol refers to the aerodynamic diameter for which half the particulate mass of the aerosol is contributed by particles with an aerodynamic diameter larger than the MMAD and half by particles with an aerodynamic diameter smaller than the MMAD.

10 “Organic acid” refers to a compound, generally of less than 300 grams/mole of molecular weight, containing one or more carboxylic acid functional groups.

“Organic acid decomposition product” refers to products resulting from a chemical modification of the organic acid. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without
15 limitation, oxidation or decarboxylation.

“Rate of aerosol formation” refers to the mass of aerosolized particulate matter produced by an inhalation device per unit time.

“Rate of inhalable aerosol particle formation” refers to the number of particles of size between 100 nm and 5 microns produced by an inhalation device per unit time.

20 “Rate of drug amine aerosol formation” refers to the mass of aerosolized, drug amine produced by an inhalation device per unit time.

“Settling velocity” refers to the terminal velocity of an aerosol particle undergoing gravitational settling in air.

“Suitable drug amine salt” refers to a drug amine salt that, when subjected to the
25 assay described in Example 2, provides a drug amine aerosol in greater than 85% purity.

“Thermal vapor” refers to a vapor phase, aerosol phase or mixture of aerosol-vapor phases, formed preferably by heating. The thermal vapor may comprise a drug and optionally a carrier, and may be formed by heating the drug and optionally a carrier.

“Treatment” refers to an approach for obtaining beneficial or desired clinical
30 results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: alleviation of symptoms, diminishment of extent of a disease, stabilization (i.e., not worsening) of a state of disease, preventing spread (i.e., metastasis) of disease, preventing occurrence or recurrence of disease, delay or slowing of disease progression, amelioration of the disease state, and remission (whether
35 partial or total).

“Typical patient tidal volume” refers to 1 L for an adult patient and 15 mL/kg for a pediatric patient.

“Vapor” refers to a gas, and “vapor phase” refers to a gas phase.

II. CHARACTERISTICS OF THE AMINE DRUG SALTS

5 Preferably, the drug amine salt is a salt of a drug amine freebase, wherein the salt of the freebase has a molecular weight of greater than 200 grams/mole. More preferably, the drug amine salt has a molecular weight greater than 250 grams/mole, 300 grams/mole, or 350 grams/mole.

10 Preferably, the drug amine salt has a decomposition index less than 0.15. More preferably, the drug amine salt has a decomposition index less than 0.10. Most preferably, the drug amine salt has a decomposition index less than 0.05. Preferably, the composition that is heated comprises at least 10 percent by weight of drug amine salt. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine salt.

15 Typically, the drug amine salt is a salt of a drug amine from one of the following classes: antibiotics, anticonvulsants, antidepressants, antiemetics, antihistamines, antiparkinsonian drugs, antipsychotics, anxiolytics, drugs for erectile dysfunction, drugs for migraine headaches, drugs for the treatment of alcoholism, drugs for the treatment of addiction, muscle relaxants, nonsteroidal anti-inflammatories, opioids, and other analgesics.

20 Typically, where the drug amine salt is a salt of an antibiotic, it is selected from a salt of one of the following compounds: cephalixin; cephaloglycin; cephalosporins, such as cephalosporin C; cephadrine; amoxicillin; hetacillin; cyclacillin; and penicillins, such as penicillin N.

Typically, where the drug amine salt is a salt of an anticonvulsant, it is selected from a salt of one of the following compounds: gabapentin, tiagabine, and vigabatrin.

Typically, where the drug amine salt is a salt of an anticonvulsant, it is selected from a salt of tiagabine.

30 Typically, where the drug amine salt is a salt of an antidepressant, it is selected from a salt of one of the following compounds: amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dosulepin, doxepin, imipramine, lofepramine, medifoxamine, mianserin, mirtazapine, nortriptyline, protriptyline, trimipramine, viloxazine, citalopram, cotinine, duloxetine, fluoxetine, fluvoxamine, milnacipran, paroxetine, reboxetine, 35 sertraline, tianeptine, iproniazid, isocarboxazid, moclobemide, phenylhydrazine,

phenelzine, selegiline, sibutramine, tranlycypromine, ademetionine, amisulpride, amperozide, benactyzine, bupropion, idazoxan, metralindole, milnacipran, minaprine, nefazodone, nomifensine, ritanserin, roxindole, tofenacin, trazodone, tryptophan, and venlafaxine.

- 5 Typically, where the drug amine salt is a salt of an antiemetic, it is selected from a salt of one of the following compounds: alizapride, azasetron, benzquinamide, bromopride, buclizine, chlorpromazine, cinnarizine, clebopride, cyclizine, diphenhydramine, diphenidol, dolasetron, droperidol, granisetron, hyoscine, metoclopramide, metopimazine, ondansetron, perphenazine, promethazine, 10 prochlorperazine, scopolamine, triethylperazine, trifluoperazine, triflupromazine, trimethobenzamide, and tropisetron.

- Typically, where the drug amine salt is a salt of an antihistamine, it is selected from a salt of one of the following compounds: azatadine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexmedetomidine, diphenhydramine, doxylamine, 15 hydroxyzine, cetirizine, fexofenadine, and promethazine.

- Typically, where the drug amine salt is a salt of an antiparkinsonian drug, it is selected from a salt of one of the following compounds: amantadine, baclofen, biperiden, benztropine, orphenadrine, procyclidine, trihexyphenidyl, levodopa, carbidopa, selegiline, deprenyl, apomorphine, benserazide, bromocriptine, budipine, cabergoline, 20 dihydroergokryptine, pramipexole, galanthamine, lazabemide, lisuride, memantine, mofegiline, pergolide, remacemide, and terguride.

- Typically, where the drug amine salt is a salt of an antipsychotic, it is selected from a salt of one of the following compounds: acetophenazine, alizapride, amperozide, benperidol, benzquinamide, bromperidol, butaperazine, carphenazine, carpipramine, 25 chlorpromazine, chlorprothixene, clocapramine, clomacran, clopenthixol, clospirazine, clothiapine, cyamemazine, droperidol, flupenthixol, fluphenazine, fluspirilene, haloperidol, mesoridazine, metofenazate, molindone, penfluridol, pericyazine, perphenazine, pimozide, pipamerone, piperacetazine, pipotiazine, prochlorperazine, promazine, remoxipride, sertindole, spiperone, sulpiride, thioridazine, thiothixene, trifluoperidol, triflupromazine, 30 trifluoperazine, ziprasidone, zotepine, zuclopenthixol, amisulpride, clozapine, melperone, olanzapine, quetiapine, and risperidone.

- Typically, where the drug amine salt is a salt of an anxiolytic, it is selected from a salt of one of the following compounds: diazepam, alprazolam, triazolam, indiplon, zaleplon, mecloqualone, medetomidine, metomidate, adinazolam, chlordiazepoxide, 35 clobenzepam, flurazepam, loprazolam, midazolam, azacyclonol, buspirone, captodiamine,

enciprazine, flesinoxan, ipsapirone, lesopitron, loxapine, methaqualone, propanolol, tandospirone, trazadone, zopiclone, and zolpidem.

Typically, where the drug amine salt is a salt of a drug for erectile dysfunction, it is selected from a salt of one of the following compounds: cialis (IC351), sildenafil,

5 vardenafil, apomorphine, apomorphine diacetate, phentolamine, and yohimbine.

Typically, where the drug amine salt is a salt of a drug for migraine headache, it is selected from a salt of one of the following compounds: almotriptan, alpiropride, eletriptan, codeine, dihydroergotamine, ergotamine, eletriptan, frovatriptan, isometheptene, lidocaine, lisuride, metoclopramide, naratriptan, oxycodone, propoxyphene, rizatriptan, 10 sumatriptan, tolfenamic acid, zolmitriptan, amitriptyline, atenolol, clonidine, cyproheptadine, diltiazem, doxepin, fluoxetine, lisinopril, methysergide, metoprolol, nadolol, nortriptyline, paroxetine, pizotiline, propanolol, protriptyline, sertraline, timolol, and verapamil.

Typically, where the drug amine salt is a salt of a drug amine for the treatment of 15 alcoholism, it is selected from a salt of one of the following compounds: naloxone, and naltrexone.

Typically, where the drug amine salt is a salt of a drug amine for the treatment of addiction it is buprenorphine.

Typically, where the drug amine salt is a salt of a muscle relaxant, it is selected 20 from a salt of one of the following compounds: baclofen, cyclobenzaprine, orphenadrine, quinine, and tizanidine.

Typically, where the drug amine salt is a salt of a nonsteroidal anti-inflammatory, it is selected from a salt of one of the following compounds: aceclofenac, alminoprofen, amfenac, bromfenac, carprofen, cinchophen, diclofenac, etodolac, mazipredone, 25 meclofenamate, pirofen, and tolfenamate.

Typically, where the drug amine salt is a salt of an opioid, it is selected from a salt of one of the following compounds: alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, cipramadol, clonitazene, codeine, dextromoramide, dextropropoxyphene, diamorphine, dihydrocodeine, 30 diphenoxylate, dipipanone, fentanyl, hydromorphone, lofentanil, levorphanol, meperidine, methadone, meptazinol, metopon, morphine, nalbuphine, nalorphine, oxycodone, papaveretum, pethidine, pentazocine, phenazocine, remifentanyl, sufentanyl, and tramadol.

Typically, where the drug amine salt is a salt of an other analgesic it is selected from a salt of one of the following compounds: apazone, benzpiperylon, benzydramine,

caffeine, clonixin, ethoheptazine, flupirtine, nefopam, orphenadrine, propacetamol, and propoxyphene.

Typically, where the drug amine salt is a salt of a stimulant, it is selected from a salt of one of the following compounds: amphetamine, brucine, caffeine, dexfenfluramine, dextroamphetamine, ephedrine, fenfluramine, mazindol, methyphenidate, pemoline, phentermine, and sibutramine.

Typically, the drug amine salt is a hydrochloric acid salt, hydrobromic acid salt, formic acid salt, acetic acid salt, maleic acid salt, fumaric acid salt, benzoic acid salt or trifluoroacetic acid salt.

Typically, the drug amine salt is selected from a group of salts consisting of brompheniramine maleate, carbinoxamine maleate, chlorpheniramine maleate, cyproheptadine hydrochloride, pyrilamine maleate, bupropion hydrochloride, trimipramine maleate, tranlycypromine hydrochloride, protriptyline hydrochloride, apomorphine diacetate hydrochloride, buprenorphine hydrochloride, nicotine dihydrochloride, nicotine sulfate, apomorphine hydrochloride, diphenhydramine hydrochloride, mexiletine hydrochloride, and nicotine hydrochloride..

Typically, the drug amine salt is a mono- or di-salt (e.g., monohydrochloride or dihydrochloride).

III. CHARACTERISTICS OF THE THERMAL VAPOR, AEROSOL AND/OR PARTICLES

Typically, the particles comprise at least 5 percent by weight of drug amine. Preferably, the particles comprise at least 10 percent by weight of drug amine. More preferably, the particles comprise at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine.

Typically, the condensation aerosol particles have a mass of at least 0.01 mg. Preferably, the aerosol particles have a mass of at least 0.05 mg. More preferably, the aerosol particles have a mass of at least 0.10 mg, 0.15 mg, 0.2 g or 0.25 mg.

Typically, the particles comprise less than 10 percent by weight of drug amine degradation products relative to drug amine. Preferably, the particles comprise less than 5 percent by weight of drug amine degradation products relative to drug amine. More preferably, the particles comprise 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of drug amine degradation products relative to drug amine.

Typically, the particles comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent, 60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

5 Typically, the particles of the delivered condensation aerosol have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass median aerodynamic diameter of less than 3 micrometers. More preferably, the particles have a mass median aerodynamic diameter between the range of 1-3 micrometers.

10 Typically, the particles of the delivered condensation aerosol have a mass median aerodynamic diameter of greater than 0.01 micrometers. Preferably, the particles have a mass median aerodynamic diameter of greater than 1 micrometers.

Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3. Preferably, the geometric standard deviation is less than 2.5. More preferably, the geometric standard deviation is less than 2.3, 2.0, 2.0 or 1.8.

15 Typically, the delivered aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 100 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 75 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 50 mg/L.

20 Typically, the delivered aerosol has an inhalable aerosol particle density greater than 10^6 particles/mL. Preferably, the aerosol has an inhalable aerosol particle density greater than 10^7 particles/mL or 10^8 particles/mL.

Typically, the rate of inhalable aerosol particle formation of the delivered condensation aerosol is greater than 10^8 particles per second. Preferably, the aerosol is formed at a rate greater than 10^9 inhalable particles per second. More preferably, the aerosol is formed at a rate greater than 10^{10} inhalable particles per second.

25 Typically, the delivered condensation aerosol is formed at a rate greater than 0.5 mg/second. Preferably, the aerosol is formed at a rate greater than 0.75 mg/second. More preferably, the aerosol is formed at a rate greater than 1 mg/second, 1.5 mg/second or 2 mg/second.

30 Typically, the thermal vapor comprises a gas and amine drug aerosol particles,
a. wherein said gas comprises an acid halide vapor, organic acid vapor, or organic acid decomposition product vapor, and

b. wherein said amine drug aerosol particles
35 i. comprise at least 10 micrograms of an amine drug and

less than 10% amine drug decomposition products relative to said total mass of amine drug in the particles, and

ii. have a mass median aerodynamic diameter in the range 1 to 5 micrometers.

5 Typically, the thermal vapor also includes supersaturated amine drug vapor. Generally, the supersaturated amine drug vapor is at a temperature greater than 200°C. More preferably, the temperature of the supersaturated amine drug vapor is greater than 300 °C.

10 Preferably, the composition that is heated comprises at least 10 percent by weight of drug amine salt. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine salt.

15 A number of gases can be used in the invention, including but not limited to air, nitrogen, argon, and carbon dioxide. The preferred embodiment includes air as a gas.

Typically, between 0.1 mg and 100 mg of drug amine are delivered to the mammal in a single inspiration. Preferably, between 0.1 mg and 75 mg of drug amine are delivered to the mammal in a single inspiration. More preferably, between 0.1 mg and 50 mg of drug amine are delivered in a single inspiration.

20 Typically, the delivered condensation aerosol results in a peak plasma concentration of drug amine in the mammal in less than 1 h. Preferably, the peak plasma concentration is reached in less than 0.5 h. More preferably, the peak plasma concentration is reached in less than 0.2, 0.1, 0.05, 0.02 or 0.01 h.

25 IV. METHODS

Selection of Drug Amine Salts for Condensation Aerosols

In one aspect the present invention provides a method of selecting an amine drug salt suitable for use in forming a condensation aerosol, comprising

- a. dissolving or suspending an amine drug salt in a solvent,
 - 30 b. coating the suspended or dissolved amine drug salt on a substrate,
 - c. heating the coated substrate to form a compound vapor,
 - d. cooling the vapor to form aerosol particles,
 - e. collecting the aerosol particles,
 - f. analyzing the collected particles to determine the purity of the aerosol
- 35 particles; and

g, selecting the amine drug based on a decomposition index less than 0.15.

Substrates on which the composition is heated are of a variety of shapes.

Examples of such shapes include, without limitation, cylinders of less than 1.0 mm in diameter, boxes of less than 1.0 mm thickness and virtually any shape permeated by small
5 (e.g., less than 1.0 mm-sized) pores. Preferably, substrates provide a large surface to volume ratio (e.g., greater than 100 per meter) and a large surface to mass ratio (e.g., greater than 1 cm² per gram).

A substrate of one shape can also be transformed into another shape with different properties. For example, a flat sheet of 0.25 mm thickness has a surface to volume ratio of
10 approximately 8,000 per meter. Rolling the sheet into a hollow cylinder of 1 cm diameter produces a support that retains the high surface to mass ratio of the original sheet but has a lower surface to volume ratio (about 400 per meter).

A number of different materials are used to construct the substrates. Classes of such materials include, without limitation, metals, inorganic materials, and polymers. The
15 following are examples of the material classes: aluminum, silver, gold, stainless steel, copper and tungsten; silica, glass, silicon and alumina; graphite; polytetrafluoroethylene and polyethylene glycol. Combinations of materials and coated variants of materials are used as well.

Where aluminum is used as a solid support, aluminum foil is a suitable material.
20 Examples of silica, alumina and silicon based materials include amorphous silica S-5631 (Sigma, St. Louis, MO), BCR171 (an alumina of defined surface area greater than 2 m²/g from Aldrich, St. Louis, MO) and a silicon wafer as used in the semiconductor industry. Chromatography resins such as octadecyl silane chemically bonded to porous silica are exemplary coated variants of silica.

25 In a preferred embodiment of the invention, the substrate is metallic. In more preferred embodiments, the substrate is aluminum foil or stainless steel.

The heating of the drug amine salt compositions is performed using any suitable method. Examples of methods by which heat can be generated include the following:
30 passage of current through an electrical resistance element; absorption of electromagnetic radiation, such as microwave or laser light; and, exothermic chemical reactions, such as exothermic solvation, hydration of pyrophoric materials, oxidation of combustible materials and heating on a hot plate.

The substrate is typically heated to a temperature of at least 200 °C to vaporize the amine drug salt. In more preferred embodiments, the substrate is heated to at least 300 °C,
35 350 °C, or 400 °C.

The particles are collected by means known to those of skill in the art; preferred means include collection in a vial or on a filter.

The resultant particles are analyzed by any technique known by those of skill in the art., including those disclosed below under Analysis of Drug Amine Aerosols. Preferred
5 methods of analyses include reverse-phase HPLC by absorption of UV light, typically at 225 nm and LC/MS.

A drug amine salt was preferred for aerosolization where the purity of the drug isolated by this method was greater than 85%. Such a drug amine salt has a decomposition index less than 0.15. The decomposition index was arrived at by subtracting the fractional
10 purity (*i.e.*, 0.85) from 1.

Formation and Delivery of Drug Amine Containing Aerosols

Any suitable vaporization method is used to form the aerosols of the present invention. A preferred method, however, involves heating a thin coating or film of a
15 composition comprising a drug amine salt to form a vapor, followed by cooling of the vapor such that it condenses to provide a drug amine comprising aerosol (condensation aerosol). The composition is heated in one of two forms: as pure active compound (*i.e.*, pure drug amine salt); or, as a mixture of active compound and a pharmaceutically acceptable excipient.

Typically, upon heating of the composition, in addition to vaporizing the drug
20 amine, the acidic component of the salt or a decomposition product thereof is also vaporized. For example, upon heating of a salt of a drug amine and an acid, wherein there is an equilibrium between the cationic drug amine plus the anionic acid and the neutral form of the drug amine plus the neutral acid, the acid may vaporize leaving behind the
25 freebase (neutral form) of the drug amine which subsequently vaporizes. Such vaporization may occur at a greater rate if the equilibrium results in a comparatively larger amount of the neutral form of the drug amine and acid, and if the neutral form of the acid has a high vapor pressure (e.g., HCl). As such, in a preferred embodiment of the invention, the acid component of the drug salt is selected to favor such an equilibrium, or is selected
30 for its high vapor pressure. In cases where the acid component of the drug amine salt is an organic acid, an alternative series of events may occur, which involves decarboxylation of the organic acid to form carbon dioxide plus organic acid decomposition products. Such decarboxylation may leave behind the drug amine in its freebase (neutral) form which may subsequently vaporize. In the case where the organic acid is, for example, lactic or tartaric
35 acid or pyruvic acid, the acid may decompose to generate acetaldehyde in addition to

carbon dioxide. In preferred embodiments of the invention the counterion degrades to form carbon dioxide. In other preferred embodiments, the counterion boils at less than 50°C, less than 100 °C , or less than 200 °C.

- In a particularly preferred embodiment, an amine drug aerosol is formed and delivered by a method, comprising:
- a. heating a coating, which includes an amine drug salt on a substrate contained in a device to a temperature sufficient to volatilize the amine drug from the coating,
 - b. by said heating, forming a amine drug vapor, and
 - c. during said heating, drawing air through said device, condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound.

To deliver a compound through the thermal aerosol route without significant thermal decomposition prior to vaporizing, a key component of the invention involves the use of a coating of the drug as a thin film prior to vaporizing it. Such thin film coatings generally result in vaporization of drug salt amines without substantial decomposition, with thinner coatings generally resulting in less decomposition than thicker coatings. In general, coatings in the range of thickness from 0.05 to 50 micrometers are preferred, with coatings in the range of thickness of 0.1 to 30 micrometers more preferred, and 0.2 to 20 micrometers most preferred. Coatings at the thinner end of the ranges are preferred for drug amines with a substantial tendency to decompose upon heating, whereas the thicker coatings can be employed for drug amines with less tendency to decompose upon heating.

In addition, certain drug amines may undergo decomposition reactions that occur substantially more rapidly in the liquid phase than in the solid phase. For such drug amines, it is particularly preferred to form amine drug salts that sublime upon heating. In a preferred embodiment of the invention, the drug salt amine sublimates at greater than 0.001 atm, 0.01 atm, 0.1 atm, or 1 atm of pressure.

Preferably, the drug amine salt used in the methods of the invention has a decomposition index less than 0.10. More preferably, the drug amine salt has a decomposition index less than 0.05. Preferably, the composition that is heated comprises at least 10 percent by weight of drug amine salt. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine salt.

Pharmaceutically acceptable excipients that are volatile or nonvolatile may be included in compositions of the methods. Volatile excipients, when heated, are concurrently volatilized, aerosolized and inhaled with drug amine. Classes of such excipients are known in the art and include, without limitation, gaseous, liquid and solid solvents. The following is a list of exemplary carriers within the classes: water; terpenes, such as menthol; alcohols, such as ethanol, propylene glycol, glycerol and other similar alcohols; dimethylformamide; dimethylacetamide; wax;; and mixtures thereof.

Substrates on which the composition is heated are of a variety of shapes. Examples of such shapes include, without limitation, cylinders of less than 1.0 mm in diameter, boxes of less than 1.0 mm thickness and virtually any shape permeated by small (*e.g.*, less than 1.0 mm-sized) pores. Preferably, substrates provide a large surface to volume ratio (*e.g.*, greater than 100 per meter) and a large surface to mass ratio (*e.g.*, greater than 1 cm² per gram).

A substrate of one shape can also be transformed into another shape with different properties. For example, a flat sheet of 0.25 mm thickness has a surface to volume ratio of approximately 8,000 per meter. Rolling the sheet into a hollow cylinder of 1 cm diameter produces a support that retains the high surface to mass ratio of the original sheet but has a lower surface to volume ratio (about 400 per meter).

A number of different materials are used to construct the substrates. Classes of such materials include, without limitation, metals, inorganic materials, carbonaceous materials and polymers. The following are examples of the material classes: aluminum, silver, gold, stainless steel, copper and tungsten; silica, glass, silicon and alumina; graphite; polytetrafluoroethylene and polyethylene glycol. Combinations of materials and coated variants of materials are used as well.

Where aluminum is used as a solid support, aluminum foil is a suitable material. Examples of silica, alumina and silicon based materials include amorphous silica S-5631 (Sigma, St. Louis, MO), BCR171 (an alumina of defined surface area greater than 2 m²/g from Aldrich, St. Louis, MO) and a silicon wafer as used in the semiconductor industry. Chromatography resins such as octadecyl silane chemically bonded to porous silica are exemplary coated variants of silica.

The heating of the drug amine salt compositions is performed using any suitable method. Examples of methods by which heat can be generated include the following: passage of current through an electrical resistance element; absorption of electromagnetic radiation, such as microwave or laser light; and, exothermic chemical reactions, such as

exothermic solvation, hydration of pyrophoric materials and oxidation of combustible materials.

Drug amine containing aerosols of the present invention are delivered using an inhalation device. Where the aerosol is a condensation aerosol, the device has at least three
5 elements: an element for heating a drug amine salt containing composition to form a vapor; an element allowing the vapor to cool, thereby providing a condensation aerosol; and, an element permitting inhalation of the aerosol. Various suitable heating methods are described above. The element that allows cooling is, in its simplest form, an inert passageway linking the heating means to the inhalation means. The element permitting
10 inhalation is an aerosol exit portal that forms a connection between the cooling element and the mammal's respiratory system.

One device used to deliver the drug amine containing aerosol is described in reference to Fig. 1. Delivery device 100 has a downstream chamber end 102 and an upstream chamber end 104, a drug supply unit 106, a power source 108, and a mouthpiece
15 110.

A drug amine salt composition is deposited on a surface 112 of the drug supply unit 106. Upon activation of a user activated switch 114, power source 108 initiates heating of the drug supply unit 106 (*e.g.*, through ignition of combustible fuel or passage of current through a resistive heating element). The drug amine composition volatilizes due to the
20 heating of the drug supply unit 106 and condenses to form a condensation aerosol prior to reaching the mouthpiece 110 at the downstream chamber end of the device 102. Air flow traveling from the device upstream chamber end 104 to the mouthpiece 110 carries the condensation aerosol to the mouthpiece 110, where it is inhaled.

Devices, if desired, contain a variety of components to facilitate the delivery of
25 drug amine containing aerosols. For instance, the device may include any component known in the art to control the timing of drug aerosolization relative to inhalation (*e.g.*, breath-actuation), to provide feedback to patients on the rate and/or volume of inhalation, to prevent excessive use (*i.e.*, "lock-out" feature), to prevent use by unauthorized individuals, and/or to record dosing histories.

30 **Dosage of Drug Amine Containing Aerosols**

A typical dosage of a drug amine aerosol is either administered as a single inhalation or as a series of inhalations taken within an hour or less (dosage equals sum of inhaled amounts). Where the drug amine is administered as a series of inhalations, a different amount may be delivered in each inhalation. The dosage amount of drug amine in

aerosol form is generally no greater than twice the standard dose of the drug amine given orally.

One can determine the appropriate dose of drug amine containing aerosols to treat a particular condition using methods such as animal experiments and a dose-finding (Phase I/II) clinical trial. One animal experiment involves measuring plasma concentrations of drug amine in an animal after its exposure to the aerosol. Mammals such as dogs or primates are typically used in such studies, since their respiratory systems are similar to that of a human. Initial dose levels for testing in humans is generally less than or equal to the dose in the mammal model that resulted in plasma drug levels associated with a therapeutic effect in humans. Dose escalation in humans is then performed, until either an optimal therapeutic response is obtained or a dose-limiting toxicity is encountered.

In another aspect of the invention, a method is provided for forming an effective human therapeutic inhalation dose of drug amine aerosol particles having less than 10% degradation products and a drug amine particle mass median aerodynamic diameter between about 1 and 5 micrometers, comprising:

- a) providing a drug delivery article comprising a body defining an interior flow-through chamber having upstream and down stream chamber ends and a drug supply unit contained within such chamber, wherein said drug supply unit comprises a heat-conductive substrate coated with a composition comprising at least a therapeutic amount of amine drug salt having a decomposition index less than 0.10;
- b) heating said heat-conductive substrate to a temperature of greater than 200°C over a period of less than 5 seconds, thereby producing a vapor of a therapeutic dose of said amine drug salt; and
- c) flowing a gas through said chamber thereby cooling said vapor to form drug amine aerosol particles

A number of drug delivery devices can be used including the one describe in Fig. 1 and above.

Preferably, the drug amine salt used in the method of the invention has a decomposition index less than 0.10. More preferably, the drug amine salt has a decomposition index less than 0.05. Preferably, the composition that is heated comprises at least 10 percent by weight of drug amine salt. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of drug amine salt.

The preferred coatings are those that result in vaporization of drug salt amines without substantial decomposition and are in the range of thickness from 0.05 to 50 micrometers. More preferred coatings are in the range of thickness of 0.1 to 30 micrometers, and the most preferred thickness is in the range 0.2 to 20 micrometers.

5

Analysis of Drug Amine Containing Aerosols

Purity of a drug amine containing aerosol is determined using a number of methods, examples of which are described in Sekine *et al.*, *Journal of Forensic Science* 32:1271-1280 (1987) and Martin *et al.*, *Journal of Analytic Toxicology* 13:158-162 (1989). One
10 method involves forming the aerosol in a device through which a gas flow (*e.g.*, air flow) is maintained, generally at a rate between 0.4 and 60 L/min. The gas flow carries the aerosol into one or more traps. After isolation from the trap, the aerosol is subjected to an analytical technique, such as gas or liquid chromatography, that permits a determination of composition purity.

15 A variety of different traps are used for aerosol collection. The following list contains examples of such traps: filters; glass wool; impingers; solvent traps, such as dry ice-cooled ethanol, methanol, acetone and dichloromethane traps at various pH values; syringes that sample the aerosol; empty, low-pressure (*e.g.*, vacuum) containers into which the aerosol is drawn; and, empty containers that fully surround and enclose the aerosol
20 generating device. Where a solid such as glass wool is used, it is typically extracted with a solvent such as ethanol. The solvent extract is subjected to analysis rather than the solid (*i.e.*, glass wool) itself. Where a syringe or container is used, the container is similarly extracted with a solvent.

The gas or liquid chromatograph discussed above contains a detection system (*i.e.*,
25 detector). Such detection systems are well known in the art and include, for example, flame ionization, photon absorption and mass spectrometry detectors. An advantage of a mass spectrometry detector is that it can be used to determine the structure of drug amine degradation products.

Particle size distribution of a drug amine containing aerosol is determined using any
30 suitable method in the art (*e.g.*, cascade impaction). An Andersen Eight Stage Non-viable Cascade Impactor (Andersen Instruments, Smyrna, GA) linked to a furnace tube by a mock throat (USP throat, Andersen Instruments, Smyrna, GA) is one system used for cascade impaction studies.

Inhalable aerosol mass density is determined, for example, by delivering a drug-
35 containing aerosol into a confined chamber via an inhalation device and measuring the

mass collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The volume of the chamber should approximate the tidal volume of an inhaling patient.

5 Inhalable aerosol drug amine mass density is determined, for example, by delivering a drug amine-containing aerosol into a confined chamber via an inhalation device and measuring the amount of non-degraded drug collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The
10 volume of the chamber should approximate the tidal volume of an inhaling patient. The amount of non-degraded drug amine collected in the chamber is determined by extracting the chamber, conducting chromatographic analysis of the extract and comparing the results of the chromatographic analysis to those of a standard containing known amounts of drug amine.

15 Inhalable aerosol particle density is determined, for example, by delivering aerosol phase drug amine into a confined chamber via an inhalation device and measuring the number of particles of given size collected in the chamber. The number of particles of a given size may be directly measured based on the light-scattering properties of the particles. Alternatively, the number of particles of a given size is determined by measuring
20 the mass of particles within the given size range and calculating the number of particles based on the mass as follows: Total number of particles = Sum (from size range 1 to size range N) of number of particles in each size range. Number of particles in a given size range = Mass in the size range/Mass of a typical particle in the size range. Mass of a typical particle in a given size range = $\pi D^3 \phi / 6$, where D is a typical particle diameter in the size range (generally, the mean boundary MMADs defining the size range) in microns,
25 ϕ is the particle density (in g/mL) and mass is given in units of picograms (g^{-12}).

Rate of inhalable aerosol particle formation is determined, for example, by delivering aerosol phase drug amine into a confined chamber via an inhalation device. The delivery is for a set period of time (e.g., 3 s), and the number of particles of a given size
30 collected in the chamber is determined as outlined above. The rate of particle formation is equal to the number of 100 nm to 5 micron particles collected divided by the duration of the collection time.

Rate of aerosol formation is determined, for example, by delivering aerosol phase drug amine into a confined chamber via an inhalation device. The delivery is for a set
35 period of time (e.g., 3 s), and the mass of particulate matter collected is determined by

weighing the confined chamber before and after the delivery of the particulate matter. The rate of aerosol formation is equal to the increase in mass in the chamber divided by the duration of the collection time. Alternatively, where a change in mass of the delivery device or component thereof can only occur through release of the aerosol phase particulate matter, the mass of particulate matter may be equated with the mass lost from the device or component during the delivery of the aerosol. In this case, the rate of aerosol formation is equal to the decrease in mass of the device or component during the delivery event divided by the duration of the delivery event.

Rate of drug amine aerosol formation is determined, for example, by delivering a drug amine containing aerosol into a confined chamber via an inhalation device over a set period of time (*e.g.*, 3 s). Where the aerosol is pure drug amine, the amount of drug collected in the chamber is measured as described above. The rate of drug amine aerosol formation is equal to the amount of drug ester aerosol collected in the chamber divided by the duration of the collection time. Where the drug amine containing aerosol comprises a pharmaceutically acceptable excipient, multiplying the rate of aerosol formation by the percentage of drug ester in the aerosol provides the rate of drug aerosol formation.

The drug amine containing aerosols of the present invention are typically used for the same indication for which they are given orally. For instance, baclofen would be used to treat parkinsons disease and fexofenadine would be used to treat allergy symptoms.

As will be apparent to those of skill in the art upon reading of this disclosure, the present invention provides valuable methods relating to amine drug aerosols. The above description of necessity provides a limited and merely illustrative sampling of the specific compounds, substrates, and devices features and should not be construed as limiting the scope of the invention. Other features and advantages of the invention will be apparent from the following examples and claims.

EXAMPLES

The following examples describe specific aspects of the invention to illustrate the invention and also provide a description of the methods used to select amine base salts suitable for forming condensation aerosols, and methods to generate amine drug aerosols and measure various physical properties of such aerosols to aid those of skill in the art in understanding and practicing the invention. The examples should not be construed as limiting the invention, in any manner.

Drug amine salts are typically commercially available from Sigma (www.sigma-aldrich.com), obtained in tablet form from a pharmacy and extracted, or synthesized using well known methods in the art.

5

EXAMPLE 1

General Procedure A for Volatilizing Drug Amines from Drug Amine Salts

General Procedure for the Preparation of a Coating Solution

The concentration of a solution for coating of the substrate was typically 50-200 mg/ml. The amine drug salt was dissolved in an appropriate solvent. Common solvent
10 choices included methanol, dichloromethane, and a 3:1 chloroform:methanol mixture, although DMF was used for less soluble amine drug salts and deionized water was used for amine drug salts that were insoluble in organic solvents. Occasionally sonication or heat was necessary to dissolve the compound.

15

Volatilization

A solution of drug amine salt in a minimal amount of solvent was typically coated on a piece of aluminum foil (precleaned with acetone). The solvent was allowed to evaporate. The coated foil was wrapped around a 300 watt halogen tube (Feit Electric Company, Pico Rivera, CA), which was inserted into a glass tube sealed at one end with a
20 rubber stopper. Running 60 V of alternating current (driven by line power controlled by a variac) through the bulb for 5-15 s or 90 V for 3.5-5 s afforded a thermal vapor (including aerosol), which was collected on the glass tube walls. (When desired, the system was flushed through with argon prior to volatilization.) Reverse-phase HPLC analysis with detection by absorption of UV light, generally at 225 nm, was used to determine the purity
25 of the aerosol.

EXAMPLE 2

General Procedure B for Volatilizing Drug Amines from Drug Amine Salts

Dip Coating

30 The substrate, consisting of a hollow stainless steel cylinder with thin walls, typically having a wall thickness of 0.12 mm, diameter 13 mm, and length 36 mm and conducive to resistance heating, was dip-coated with an amine drug salt coating solution (prepared as disclosed in Example 1) typically using a computerized dip-coating machine to produce a thin layer of drug on the outside of the substrate surface. Prior to using, the
35 substrates were cleaned in dichloromethane, methanol, and acetone, then dried, and fired at

least once to remove any residual volatile material. The substrate was lowered into the drug solution and then removed from the solvent at a rate of typically 5-25cm/sec. The substrate was then allowed to dry for 30 minutes inside a fume hood. If either DMF or a water mixture was used as a dip coating solvent, the substrate was vacuum dried inside a desiccator for a minimum of one hour. Once the substrate was solvent free and only the drug remained, it was ready for volatilization. The drug-coated portion of the cylinder generally has a surface area of 8.5 cm². By assuming a unit density for the drug, the initial drug coating thickness were calculated.

Volatilization

A dip coated substrate was placed in a surrounding glass tube connected at the exit end via Tygon tubing to a filter holder fitted with a Savillex Teflon filter and the junction is sealed with paraffin film. The substrate was placed in a fitting which connects it to two 1 farad capacitors wired in series and controlled by a 12-volt relay. The capacitors were charged by a separate power source to about 16-21 volts and all the power was channeled to the substrate by closing a switch and allowing the capacitors to discharge into the substrate. The substrate was heated to a temperature of ~ 400°C in ~ 50 milliseconds. This heating process was done under an airflow of 15 L/min, which swept the vaporized drug aerosol into a 2 micron Teflon filter. After volatilization, the aerosol captured on the filter was recovered for analysis. Any material deposited on the glass sleeve or remaining on the substrate was also recovered. The recovered materials were analyzed by HPLC UV absorbance, generally at 225 nm, or alternatively at 250, 275, or 280 nm, using a gradient method aimed at detection of impurities. The samples were further analyzed by LC/MS to confirm the molecular weight of the drug and any degradants.

Table 1, which follows, provides data from drug amines volatilized using the above-recited general procedures A and B.

TABLE 1

Generic Name	MW	Dose (mg)	Method	Sur-face Area	Thick-ness (μm)	Mass coated (mg)	Yield	% Pur-ity
Apomorphine HCl	304	2	B	6	1.1	0.68	0.60	98.1
Apomorphine HCl Diacetate	388	2	A	20	1.0	1.9	1.65	94

Bromphenir- amine Maleate	435	2	A	20	2.8	5.60	3.4	99.6
Bromphenir- amine Maleate	435	2	A under argon	20	3.2	6.40	3.2	100
Buprenor- phine HCl	504	0.3	A	20	1.1	2.10	1.37	91.4
Buprenor- phine HCl	504	0.3	A	20	0.05	0.1	0.08	98.0
Bupropion HCl	276	100	A	20	1.1	2.30	2.1	98.5
Bupropion HCl	276	100	A under argon	20	1.1	2.30	1.8	99.1
Buspirone HCl	422	15	A	20	4.2	8.30	2.42	97.8
Carbinox- amine Maleate	407	4	A	20	3.9	7.70	4.8	99
Carbinox- amine Maleate	407	4	A under argon	20	3.4	6.8	3.0	100
Chlorphenir- amine Maleate	391	8	A	20	1.6	3.20	2.1	99.6
Chlorphenir- amine Maleate	391	8	A under argon	20	2.1	4.2	2.1	100
Clemastine Fumarate	460	1.34	A	20	2.9	5.70	1.8	76.6
Cyprohepta- dine HCl	324	4	A	20	2.2	4.30	2.6	99.6
Cyprohepta- dine HCl	324	4	A under argon	20	1.8	3.5	2.1	99.6

Diphenhydr- amine HCl	292	25	A	20	2.5	4.9	3.7	90.3
Diphenhydr- amine HCl	292	25	A under argon	20	2.6	5.2	3.9	93.3
Enalapril maleate	493	5	B	8	1.1	0.85	0.29	61.0
Fluphenazine 2HCl	510	1	B	8	1.0	0.78	0.33	80.7
Hydroxyzine 2HCl	448	50	A	20	13.7	27.30	0.25	41.2
Hydroxyzine 2HCl	448	50	A under argon	20	12.8	25.60	1.4	70.8
Meclizine 2HCl	464	25	A	20	9.7	19.40	0.5	75.3
Meclizine 2HCl	464	25	A under argon	20	11.7	23.40	0.4	70.9
Mexiletine HCl	216	200	B	8	0.9	0.75	0.44	99.4
Nicotine HCl	198	1	A	32	3.2	10.3	5.4	99.9
Nicotine 2HCl	235	1	A	32	4.6	14.8	12.9	99.5
Nicotine Sulfate	260	1	A	32	2.5	8.0	1.8	97.0
Prochlorpera- zine 2HCl	446	5	B	8	0.8	0.65	0.24	72.4
Protriptyline HCl	299	15	A	20	1.1	2.20	0.99	99.7
Protriptyline HCl	299	15	A under argon	20	1.1	2.1	1.1	99.8
Pyrilamine Maleate	401	25	A	20	10.8	21.50	10.5	93.7

Pyrilamine Maleate	401	25	A under argon	20	10.2	20.4	9.6	90.7
Tranlycypromine HCl	169	30	A	20	1.2	2.30	1.3	97.5
Tranlycypromine HCl	169	30	A under argon	20	1.0	2.0	1.2	97.2
Trifluoperazine 2HCl	480	7.5	B	8	1.2	0.97	0.52	87.5
Trimipramine Maleate	411	50	A	20	1.2	2.40	1.6	95.9
Trimipramine Maleate	411	50	A under argon	20	1.1	2.20	2.1	97.4

EXAMPLE 3

General Procedure A for Screening Drug Amine Salts for Aerosolization Preferability

Drug amine salt (1 mg) was dissolved or suspended in a minimal amount of solvent, such as for example, methanol. The solution or suspension was pipetted onto the middle portion of a 3 cm by 3 cm piece of aluminum foil. The coated foil was wrapped around the end of a 1½ cm diameter vial and secured with parafilm. A hot plate was preheated to approximately 300 °C, and the vial was placed on it foil side down. The vial was left on the hotplate for 10 s after volatilization or decomposition had begun. After removal from the hotplate, the vial was allowed to cool to room temperature. The foil was removed, and the vial was extracted with dichloromethane followed by saturated aqueous NaHCO₃. The organic and aqueous extracts were shaken together, separated, and the organic extract is dried over Na₂SO₄. An aliquot of the organic solution was removed and injected into a reverse-phase HPLC with detection by absorption of UV light, generally at 225 nm. A drug amine salt was preferred for aerosolization where the purity of the drug isolated by this method was greater than 85%. Such a drug amine salt has a decomposition index less than 0.15. The decomposition index was arrived at by subtracting the fractional purity (*i.e.*, 0.85) from 1.

EXAMPLE 4

General Procedure B for Screening Drug Amine Salts for Aerosolization Preferability

Volatilizations were done using a setup which consists of two 1 farad capacitors wired in series and controlled by a 12-volt relay. A dip coated substrate (prepared as described in Example 2) was placed in a surrounding tube connected at the exit end via Tygon tubing to a filter holder fitted with a Savillex Teflon filter and the junction is sealed with paraffin film. The substrate was placed in a fitting which connects it to the capacitors. The capacitors were charged by a separate power source to about 16-21 volts and all the power was channeled to the substrate by closing a switch and allowing the capacitors to discharge into the substrate. The substrate was heated to a temperature of $\sim 400^{\circ}\text{C}$ in ~ 50 milliseconds. This heating process was done under an airflow of 15 L/min, which swept the vaporized drug aerosol into a 2 micron Teflon filter. After volatilization, the aerosol captured on the filter was recovered for analysis. Any material deposited on the glass sleeve or remaining on the substrate was also recovered. The recovered materials were analyzed by HPLC UV absorbance, generally at 225 nm, or alternatively at 250, 275, or 280 nm, using a gradient method aimed at detection of impurities. The samples were further analyzed by LC/MS to confirm the molecular weight of the drug and any degradants. A drug amine salt was preferred for aerosolization where the purity of the drug isolated by this method was greater than 85%. Such a drug amine salt has a decomposition index less than 0.15. The decomposition index was arrived at by subtracting the fractional purity (*i.e.*, 0.85) from 1.

EXAMPLE 5

Particle Size, Particle Density, and

Rate of Inhalable Particle Formation of Amine Drug Aerosol

A solution of 50-200 mg of amine drug salt per mL of solvent was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The solvent was allowed to evaporate. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were sealed with parafilm, which was punctured with fifteen needles for air flow. The third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 3.5-6 s. The aerosol was analyzed by connecting the 1 L flask to an eight-stage Andersen non-viable cascade impactor. MMAD of the collected aerosol ranged between 1 and 3 microns with a

geometric standard deviation of less than 3. The number of particles collected on the various stages of the cascade impactor was given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle, $\pi D^3/6$, multiplied by the density of the drug (taken to be 1 g/cm³). The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L. The rate of inhalable aerosol particle formation is the sum of the numbers of particles collected on impactor stages 3 through 8 divided by the formation time.

10

EXAMPLE 6

Drug Mass Density of Amine Drug Aerosol From Amine Drug Salts

A solution of 50-200 mg of amine drug salt per mL of solvent was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The solvent was allowed to evaporate. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were sealed with parafilm, which was punctured with fifteen needles for air flow. The third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within seconds, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with formation of the aerosol terminated after about 3.5-5 s. The aerosol was allowed to sediment onto the walls of the 1 L flask for approximately 30 minutes. The flask was then extracted with acetonitrile and the extract analyzed by HPLC with detection by light absorption at 225 nm. Comparison with standards containing known amounts of the amine drug revealed the purity of the amine drug that had been collected in the flask, resulting in a calculatable aerosol drug mass density.

Although certain embodiments and examples have been used to describe the present invention, it will be apparent to those of skill in the art that changes may be made to those described embodiments and examples without departing from the scope or spirit of the invention of the following claims.

What is Claimed:

1. A method of selecting an amine drug salt suitable for use in forming a condensation aerosol, comprising
 - a. dissolving or suspending an amine drug salt in a solvent,
 - 5 b. coating the suspended or dissolved amine drug salt on a substrate,
 - c. heating the coated substrate to form a compound vapor,
 - d. cooling the vapor to form aerosol particles,
 - e. collecting the aerosol particles,
 - f. analyzing the collected particles to determine the purity of the aerosol
 - 10 particles; and
 - g. selecting the amine drug based on a decomposition index less than 0.15.
2. The method of Claim 1, wherein said substrate is metallic.
- 15 3. The method of Claim 2, wherein said metallic substrate is aluminum foil or stainless steel.
4. The method of Claim 2, wherein said heating is on a hot plate.
- 20 5. The method of Claim 4, wherein said heating is to a temperature approximately about 300 °C.
6. The method of Claim 1, wherein said heating is resistance heating.
- 25 7. The method of Claim 6, wherein said heating is to a temperature of approximately about 400 °C.
8. The method of Claim 1, wherein the amine drug salt is selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for erectile dysfunction, a drug for migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.
- 30 9. An aerosol comprising an amine drug from an amine drug salt selected by the method of Claim 2, wherein said amine drug salt is vaporized and condensed to form
- 35

amine drug aerosol particles having a mass median aerodynamic diameter between the range of 1 and 3, and has less than 10% amine drug decomposition products.

10. The aerosol of Claim 9, wherein said amine drug salt has a molecular
5 weight between 200 to 600.

11. The aerosol of Claim 9, wherein said amine drug salt is selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for erectile dysfunction, a drug for
10 migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.

12. A method of delivering an amine drug in an aerosol form, comprising
a. heating a coating, which includes an amine drug salt on a substrate
15 contained in a device to a temperature sufficient to volatilize the amine drug from the coating,
b. by said heating, forming a amine drug vapor, and
c. during said heating, drawing air through said device, condensing said vapor to form aerosol particles containing less than 10% degradation products of the compound.
20

13. The method according to claim 12, wherein said coating of amine drug salt has a thickness between about 0.2 and 20 μm .

14. The method according to Claim 13, wherein said aerosol particles have a
25 mass median aerodynamic diameter between about 1 and 3 microns.

15. The method of Claim 14, wherein the amine drug salt is selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for erectile dysfunction, a drug for
30 migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.

16. The method according to claim 15, wherein said amine drug salt has a molecular weight between 200 to 600.
35

17. A thermal vapor comprising gas and amine drug aerosol particles,
- a. wherein said gas comprises an acid halide vapor, organic acid vapor, or organic acid decomposition product vapor, and
- b. wherein said amine drug aerosol particles
- 5 i. comprise at least 10 micrograms of an amine drug and less than 10% amine drug decomposition products relative to said total mass of amine drug in the particles, and
- ii. have a mass median aerodynamic diameter in the range 1 to 5 micrometers.
- 10 18. The thermal vapor of Claim 17, wherein said gas further comprises supersaturated drug amine vapor.
19. The thermal vapor of Claim 18, wherein said supersaturated drug amine vapor
- 15 has a temperature of greater than 200°C.
20. The thermal vapor of Claim 17, wherein said drug amine aerosol particles have a mass median aerodynamic diameter in the range 1 to 3 micrometers.
- 20 21. The thermal vapor of Claim 17, wherein the amine drug is selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for erectile dysfunction, a drug for migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.
- 25 22. A method of forming an effective human therapeutic inhalation dose of drug amine aerosol particles having less than 10% degradation products and a drug amine particle mass median aerodynamic diameter between about 1 and 5 micrometers, comprising
- 30 a) providing a drug delivery article comprising a body defining an interior flow-through chamber having upstream and down stream chamber ends and a drug supply unit contained within such chamber, wherein said drug supply unit comprises a heat-conductive substrate coated with a composition comprising at least a therapeutic amount of amine drug salt having a decomposition index less than 0.10;

b) heating said heat-conductive substrate to a temperature of greater than 200°C over a period of less than 5 seconds, thereby producing a vapor of a therapeutic dose of said amine drug salt; and

5 c) flowing a gas through said chamber thereby cooling said vapor to form drug amine aerosol particles.

23. The method according to Claim 22, wherein the drug amine salt is a salt selected from the group consisting of an antibiotic, anticonvulsant, antidepressant, antiemetic, antihistamine, antiparkinsonian drug, antipsychotic, anxiolytic, a drug for
10 erectile dysfunction, a drug for migraine headache, a drug for the treatment of addiction, a muscle relaxant, a non-steroidal anti-inflammatory, an opioid, or other analgesic.

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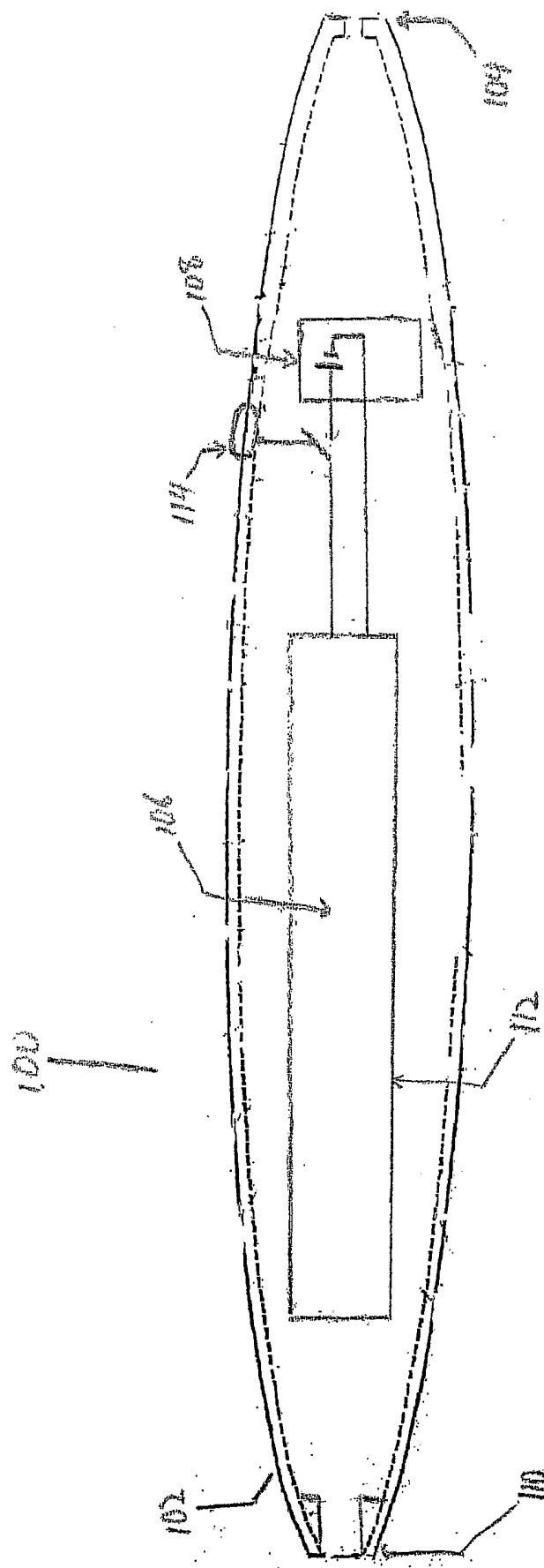


Fig.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/14976

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/72 A61M15/00

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)
IPC 7 A61K A61M

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, PAJ, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MENG YUN ET AL: "Pharmacological effects of methamphetamine and other stimulants via inhalation exposure." DRUG AND ALCOHOL DEPENDENCE, vol. 53, no. 2, 7 January 1999 (1999-01-07), pages 111-120, XP002255929 ISSN: 0376-8716 abstract paragraphs '02.3!, '02.5!, '03.1! page 118, right-hand column, last paragraph -page 119, left-hand column, paragraph 1</p> <p style="text-align: center;">--- -/-</p>	<p>9-11, 17-21</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "C" 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

29 September 2003

Date of mailing of the international search report

17/10/2003

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Epskamp, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/14976

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 735 217 A (MUCKENFUHS DELMAR R ET AL) 5 April 1988 (1988-04-05) column 3, line 45 -column 4, line 8 column 6, line 33 - line 50 column 8, line 43 - line 63 claims 1-6 ---	1-23
X	WO 94 09842 A (ROSEN CHARLES A) 11 May 1994 (1994-05-11) page 5, line 30 -page 6, line 31 page 21, line 14 - line 21 page 21, line 18 -page 22, line 22 ---	1-23
P,X	WO 02 098389 A (ALEXZA MOLECULAR DELIVERY CORP) 12 December 2002 (2002-12-12) page 1, line 28 -page 2, line 28 page 15, line 13 - line 30 example 9 claims ---	1-23
P,X	WO 02 094231 A (ALEXZA MOLECULAR DELIVERY CORP) 28 November 2002 (2002-11-28) paragraphs '0063!', '0064! example 2 claims ---	1-23
P,X	WO 02 094232 A (ALEXZA MOLECULAR DELIVERY CORP) 28 November 2002 (2002-11-28) paragraphs '0180!', '0181! example 2 claims ---	1-23
P,X	WO 03 026631 A (ALEXZA MOLECULAR DELIVERY CORP) 3 April 2003 (2003-04-03) example 5 claims -----	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/14976

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:

Although claims 12-16, 22 and 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers 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.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Information on patent family members

PCT/US 03/14976

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/14976

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Information on patent family members

International Application No

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