METHOD, DEVICE, AND SYSTEM TO CONTROL pH IN PULMONARY TISSUE OF A SUBJECT

Inventors: Roderick A. Hyde, Redmond, WA (US); Muriel Y. Ishikawa, Livermore, CA (US); Jordin T. Kare, Seattle, WA (US); Dennis J. Rivet, Portsmouth, VA (US); Lowell L. Wood, JR., Bellevue, WA (US); Victoria Y.H. Wood, Livermore, CA (US)

Correspondence Address:
SEARETE LLC
CLARENCE T. TEGREEE
1756 - 114TH AVE., S.E., SUITE 110
BELLEVUE, WA 98004 (US)

Assignee: Searete LLC,

Appl. No.: 12/319,655

Filed: Jan. 8, 2009

Related U.S. Application Data
Continuation of application No. 12/286,752, filed on Sep. 30, 2008, which is a continuation-in-part of application No. 12/286,729, filed on Sep. 30, 2008, which is a continuation-in-part of application No. 12/286,753, filed on Sep. 30, 2008.

Publication Classification
Int. Cl.
A61B 5/091 (2006.01)
A61B 5/00 (2006.01)
A61B 5/08 (2006.01)

U.S. Cl. .................. 600/532; 600/300; 600/538

ABSTRACT
Methods, systems, and devices are provided which include receiving data or providing data, wherein the data regards a physical condition affecting one or more subjects. The data can inform administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition is configured to contact pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects. The data regarding the physical condition may be acquired prior to the subject entering an environment where the physical condition exists.
Receiving data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition is configured to contact pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects.

- a sensor located on the subject detects the sensed physical condition.
- the sensor is located in a sinus or nostril of the subject.
- the sensor is configured to monitor pH of the pulmonary tissue or pH of an exhalant in the subject.
- the sensor is configured to monitor humidity of an exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, expiratory reserve volume, or residual volume.

Wherein the physical condition affecting the one or more subjects is an environmental condition, a signal from a global positioning device, a calendar entry, an environmental forecast, or a weather forecast.

The calendar entry is configured to communicate data on the environmental condition, the environmental forecast, or the weather forecast.

Including receiving data of a physiological condition of the one or more subjects.

The calendar entry is configured to communicate data on the subject's physiological condition.

The global positioning device is configured to communicate data on a location of the one or more subjects.
FIG. 3B

A third party advises or controls the administration of the pharmaceutical composition to the one or more subjects 305

Further comprising providing data including the data of the physical condition affecting one or more subjects 306

The pharmaceutical composition includes at least one agent and is configured to achieve a selected pH range of the pulmonary tissue of the one or more subjects 307

The at least one agent is at least one buffering agent, at least one basic agent, or at least one acidic agent 318

The pulmonary disease or condition is a viral pulmonary disease or a bacterial pulmonary disease 308

The one or more subjects are mammalian or avian 309

The pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject 319

The pharmaceutical composition includes a first agent in first-sized particles configured to maintain a first pH range in a first level of pulmonary tissue of the subject, and a second agent in second-sized particles configured to maintain a second pH range in a second level of pulmonary tissue of the subject 320
FIG. 4

providing data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition contacts pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects

including sensing the physical condition affecting the one or more subjects
a system including a signal-bearing medium including 501

one or more instructions for receiving data including data of a
physical condition affecting one or more subjects the data
informing administration of a pharmaceutical composition in
response to the physical condition, wherein the
pharmaceutical composition contacts pulmonary tissue to
treat a pulmonary disease or condition in one or more
subjects

FIG. 5
**FIG. 6A**

A method for treating a pulmonary viral infectious disease in a subject 601

- Administering a pharmaceutical composition including at least one charged ion to a pulmonary tissue of the subject, wherein the pharmaceutical composition includes a membrane selective for the charged ion and is configured to achieve a selected pH of the pulmonary tissue in the subject 602
  - The selected pH of the pulmonary tissue is basic; or the selected pH of the pulmonary tissue is acidic 603
  - The pharmaceutical composition including the membrane is transmitted based upon an existing pH of the pulmonary tissue 604
  - The charged ion is released based upon an existing pH of the pulmonary tissue 605
  - Membrane integrity is broken based upon an existing pH of the pulmonary tissue 606
  - The membrane selective for the charged ion includes membranes of two or more non-overlapping and distinct particle size ranges configured to contact two or more levels of pulmonary tissue of the subject 607

- The membrane is configured to alter selectivity for the charged ion in response to a sensed condition in the pulmonary tissue 608
  - A sensor is configured to monitor the condition of the subject 609
    - The sensor is configured to monitor at least one of pH of the pulmonary tissue or pH of an exhalant 610
    - The pH-monitoring sensor is in an airway passage of the subject; or the pH-monitoring sensor is in a sinus or a nostril of the subject 612
      - Including a pH-sensitive detection component in the pharmaceutical composition, the pH-sensitive detection component configured to communicate to the pH-monitoring sensor 613
      - The pH-sensitive detection component releases a marker indicating a pH range, and the pH-monitoring sensor is configured to recognize the marker 614

- The sensor is configured to monitor at least one of humidity of an exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, expiratory reserve volume, or residual volume 611
FIG. 6B

The controller is configured to deliver one or more membrane particles of the selected pH 618

The controller is configured to select a membrane particle size range 616

A controller responsive to the sensor is configured to alter the membrane selectivity for the charged ion 615

The pharmaceutical composition is administered in response to a sensed environmental condition, e.g., the sensed environmental condition includes a potentially infectious environment 619

The pulmonary tissue includes an epithelial tissue, mesenchymal tissue, or endothelial tissue, e.g., oropharynx or nasopharynx tissue, e.g., trachial, bronchial, bronchiole, alveolar duct, or alveoli tissue 620

The charged ion includes a cation, e.g., H⁺, K⁺, or Mg²⁺ 621

The charged ion includes an anion, e.g., phosphate, citrate, lactate, pyruvate, or an organic acid 622

The pharmaceutical composition includes a buffering agent, e.g., at least one of a phosphate buffer, citrate buffer, lactate buffer, pyruvate buffer, or an organic acid buffer 623
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>624</td>
<td>The pharmaceutical composition is administered orally or nasally</td>
</tr>
<tr>
<td>625</td>
<td>The pharmaceutical composition is administered as a continuous or pulsatile dose of the pharmaceutical composition</td>
</tr>
<tr>
<td>626</td>
<td>An aerosol dose of the pharmaceutical composition is delivered directly to an individual</td>
</tr>
<tr>
<td>627</td>
<td>An aerosol dose of the pharmaceutical composition is delivered to one or more individuals in an enclosed space</td>
</tr>
<tr>
<td>628</td>
<td>An aerosol dose of the pharmaceutical composition is delivered through a heating, ventilation, or air conditioning system</td>
</tr>
<tr>
<td>629</td>
<td>The pharmaceutical composition is configured to provide a timed-release of the charged ion</td>
</tr>
<tr>
<td>630</td>
<td>The pharmaceutical composition is configured to provide a slow-absorbing form of the charged ion</td>
</tr>
<tr>
<td>631</td>
<td>The pharmaceutical composition is a liquid or a powder</td>
</tr>
</tbody>
</table>
A device including:

701

an aerosol generator, and a pharmaceutical composition including a membrane selective for a charged ion configured to achieve a selected pH of a pulmonary tissue in a subject.

702
A method for treating a pulmonary viral infectious disease in a subject includes

- administering a pharmaceutical composition including at least one agent to a pulmonary tissue of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject.

- the pulmonary tissue includes e.g., epithelial tissue, mesenchymal tissue, or endothelial tissue, e.g., oropharynx or nasopharynx tissue, e.g., trachial tissue, bronchial, bronchole, alveolar duct, or alveoli tissue.

- the at least one agent is at least one buffering agent, at least one basic agent, or at least one acidic agent.

- the two or more distinct and non-overlapping particle size ranges include an anion exchange particle or a cation exchange particle.

- the two or more distinct and non-overlapping particle size ranges include powders, micronized microparticles, nanoparticles, or liposomes.

- the two or more distinct and non-overlapping particle size ranges include less than about 10 μm, less than about 6 μm, less than about 4 μm, less than about 3 μm, less than about 2 μm, less than about 1500 nm, less than about 1 micron, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm.

- at least about 70%, at least about 90%, or at least about 95% of the two or more distinct and non-overlapping particle size ranges have a particle size less than the average particle size.

- the micronized microparticle includes a pharmaceutical carrier include lactose, dextran, dextrose, or mannitol, or mixtures thereof.
FIG. 8B

the pharmaceutical composition includes a first agent in first-sized particles configured to maintain a first pH range in a first level of pulmonary tissue of the subject, and a second agent in second-sized particles configured to maintain a second pH range in a second level of pulmonary tissue of the subject 811

the first-sized particles and the second-sized particles include the two or more particle size ranges of less than about 10 μm, less than about 6 μm, less than about 4 μm, or less than about 2 μm 813

the first agent includes a buffering agent to maintain the first pH range below approximately 7.0 814

the first agent is a buffering agent configured to maintain the first pH range from approximately 7.2 to approximately 7.6 815

the second agent is a buffering agent configured to maintain the second pH range from approximately 6.4 to approximately 7.4 816

the pharmaceutical composition is administered in response to a sensed environmental condition 812

the sensed environmental condition includes a potentially infectious environment 817
FIG. 8C

the pharmaceutical composition is configured to provide a timed-release of the buffering agents 818

the pharmaceutical composition is configured to provide a slow-absorbing form of the buffering agents 820

the at least one buffering agent is linked to a viral homing entity 821

the viral homing entity binds to a surface molecule of the virus 822

the viral homing entity binds to a cell or tissue of the subject 823

the buffering agent includes phosphate buffer, citrate buffer, lactate buffer, pyruvate buffer, or an organic acid buffer 819
METHOD, DEVICE, AND SYSTEM TO CONTROL PH IN PULMONARY TISSUE OF A SUBJECT

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is related to and claims the benefit of the earliest available effective filing date(s) from the following listed application(s) (the "Related Applications") (e.g., claims earliest available priority dates for other than provisional patent applications or claims benefits under 35 USC §119(e) for provisional patent applications, for any and all parent, grandparent, great-grandparent, etc. applications of the Related Application(s)).

RELATED APPLICATIONS

[0002] For purposes of the USPTO extra-statutory requirements, the present application constitutes a continuation-in-part of U.S. patent application Ser. No. To Be Assigned, entitled METHOD, DEVICE, AND SYSTEM TO CONTROL PH IN PULMONARY TISSUE OF A SUBJECT, naming Roderick A. Hyde, Muriel Y. Ishikawa, Jordin T. Kare, Dennis J. Rivet, Lowell L. Wood, Jr., and Victoria Y. H. Wood as inventors, filed 30 Sep. 2008, which is currently co-pending, or is an application of which a currently co-pending application is entitled to the benefit of the filing date.

[0003] For purposes of the USPTO extra-statutory requirements, the present application constitutes a continuation-in-part of U.S. patent application Ser. No. To Be Assigned, entitled METHOD, COMPOSITION, AND SYSTEM TO CONTROL PH IN PULMONARY TISSUE OF A SUBJECT, naming Roderick A. Hyde, Muriel Y. Ishikawa, Jordin T. Kare, Dennis J. Rivet, Lowell L. Wood, Jr., and Victoria Y. H. Wood as inventors, filed 30 Sep. 2008, which is currently co-pending, or is an application of which a currently co-pending application is entitled to the benefit of the filing date.

[0004] The United States Patent Office (USPTO) has published a notice to the effect that the USPTO's computer programs require that patent applicants reference both a serial number and indicate whether an application is a continuation or continuation-in-part. Stephen G. Kunin, Benefit of Prior-Filed Application, USPTO Official Gazette Mar. 18, 2003, available at http://www.uspto.gov/web/offices/com/sol/og/2003/week11/parbene.htm. The present Applicant Entity (hereinafter "Applicant") has provided above a specific reference to the application(s) from which priority is being claimed as recited by statute. Applicant understands that the statute is unambiguous in its specific reference language and does not require either a serial number or any characterization, such as "continuation" or "continuation-in-part," for claiming priority to U.S. patent applications. Notwithstanding the foregoing, Applicant understands that the USPTO's computer programs have certain data entry requirements, and hence Applicant is designating the present application as a continuation-in-part of its parent applications as set forth above, but expressly points out that such designations are not to be construed in any way as any type of commentary and/or admission as to whether or not the present application contains any new matter in addition to the matter of its parent application(s).

SUMMARY

[0005] All subject matter of the Related Applications and of any and all parent, grandparent, great-grandparent, etc. applications of the Related Applications is incorporated herein by reference to the extent such subject matter is not inconsistent herewith.

[0006] Methods, systems, and devices are described herein which include receiving data or providing data, wherein the data regards a physical condition affecting one or more subjects. The data regarding the physical condition may be acquired prior to the subject entering an environment where the physical condition exists. Methods, systems, and devices are described herein which include receiving data including data of a physical condition affecting one or more subjects. Methods, systems, and devices as described herein can further include sensing the physical condition affecting the one or more subjects. The physical condition affecting the one or more subjects includes, but is not limited to, an environmental condition, a signal from a global positioning device, a calendar entry, an environmental forecast, or a weather forecast, or a combination thereof. The physical condition may further include a physiological condition of the one or more subjects. A sensor may be located on the subject which detects the sensed physical condition. The sensor may be configured to monitor pH of the pulmonary tissue or pH of an exhalant in the subject. The sensor may be configured to monitor humidity of an exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, expiratory reserve volume, or residual volume.

[0007] The pharmaceutical composition includes at least one agent, e.g., at least one buffering agent, at least one basic agent, or at least one acidic agent, or a combination thereof, and is configured to achieve a selected pH range of the pulmonary tissue of the one or more subjects. The pharmaceutical composition may be administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject.

[0008] Method are described herein which include receiving data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition is configured to contact pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects. The method may further include sensing the physical condition affecting the one or more subjects. The physical condition affecting the one or more subjects includes, but is not limited to, an environmental condition, a signal from a global positioning device, a calendar entry, an environmental forecast, or a weather forecast. The method may further include receiving data of a physiological condition of the one or more subjects. In one aspect, the calendar entry is configured to communicate data on the environmental condition, the environmental forecast, or the
weather forecast. In a further aspect, the calendar entry is configured to communicate data on the subject’s physiological condition. The data of the physical condition can be acquired prior to the subject entering an environment where the physical condition exists. The global positioning device can be configured to communicate data on a location of the one or more subjects. The sensor located on the subject may detect the sensed physical condition. The sensor may be located in a sinus or nostril of the subject. The sensor can be configured to monitor pH of the pulmonary tissue or pH of an exhalant in the subject. The sensor can be configured to monitor one or more of humidity of an exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, respiratory reserve volume, or residual volume. In one aspect, a third party advises or controls the administration of the pharmaceutical composition to the one or more subjects. The method may further comprise receiving data including the data of the physical condition affecting one or more subjects. The pharmaceutical composition may include at least one agent and is configured to achieve a selected pH range of the pulmonary tissue of the one or more subjects. The at least one agent includes, but is not limited to, at least one buffering agent, at least one basic agent, or at least one acid agent. The pharmaceutical composition may be administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject. The pharmaceutical composition can include a first agent in first-sized particles configured to maintain a first pH range in a first level of pulmonary tissue of the subject, and a second agent in second-sized particles configured to maintain a second pH range in a second level of pulmonary tissue of the subject. The pulmonary disease or condition includes, but is not limited to, a viral pulmonary disease or a bacterial pulmonary disease. The one or more subjects includes, but is not limited to, mammalian or avian.

Methods are described herein which include providing data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition contacts pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects. The method may further include sensing the physical condition affecting the one or more subjects. The physical condition affecting the one or more subjects includes, but is not limited to, an environmental condition, a signal from a global positioning device, a calendar entry, an environmental forecast, or a weather forecast. The method may further include receiving data of a physiological condition of the one or more subjects. In one aspect, the calendar entry is configured to communicate data on the environmental condition, the environmental forecast, or the weather forecast. In a further aspect, the calendar entry is configured to communicate data on the subject’s physiological condition. The data of the physical condition can be acquired prior to the subject entering an environment where the physical condition exists. The global positioning device can be configured to communicate data on a location of the one or more subjects. The sensor located on the subject may detect the sensed physical condition. The sensor may be located in a sinus or nostril of the subject. The sensor can be configured to monitor pH of the pulmonary tissue or pH of an exhalant in the subject. The sensor can be configured to monitor one or more of humidity of an exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, respiratory reserve volume, or residual volume. In one aspect, a third party advises or controls the administration of the pharmaceutical composition to the one or more subjects. The method may further comprise receiving data including the data of the physical condition affecting one or more subjects. The pharmaceutical composition may include at least one agent and is configured to achieve a selected pH range of the pulmonary tissue of the one or more subjects. The at least one agent includes, but is not limited to, at least one buffering agent, at least one basic agent, or at least one acid agent. The pharmaceutical composition may be administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject. The pharmaceutical composition can include a first agent in first-sized particles configured to maintain a first pH range in a first level of pulmonary tissue of the subject, and a second agent in second-sized particles configured to maintain a second pH range in a second level of pulmonary tissue of the subject. The pulmonary disease or condition includes, but is not limited to, a viral pulmonary disease or a bacterial pulmonary disease. The one or more subjects includes, but is not limited to, mammalian or avian.
further include instructions for sensing the physical condition affecting the one or more subjects.

[0013] Systems are described herein which include circuitry for providing data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition contacts pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects. The system may further include circuitry for sensing the physical condition affecting the one or more subjects.

[0014] Devices are described herein which include systems including a signal-bearing medium including one or more instructions for receiving data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition contacts pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects. The device may further include one or more instructions for sensing the physical condition affecting the one or more subjects. The device may further include instructions for receiving data of a physiological condition of the one or more subjects.

[0015] Devices are described herein which include systems including a signal-bearing medium including one or more instructions for providing data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition contacts pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects. The device may further include one or more instructions for sensing the physical condition affecting the one or more subjects. The device may further include instructions for providing data of a physiological condition of the one or more subjects.

[0016] The foregoing summary is illustrative only and is not intended to be in any way limiting. In addition to the illustrative aspects, embodiments, and features described above, further aspects, embodiments, and features will become apparent by reference to the drawings and the following detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0017] FIGS. 1A and 1B depict a diagrammatic view of one aspect of an exemplary embodiment of a method, device, or system that may serve as an illustrative environment for subject matter technologies.

[0018] FIGS. 2A, 2B, and 2C depict a diagrammatic view of one aspect of an exemplary embodiment of a method, device, or system that may serve as an illustrative environment for subject matter technologies.

[0019] FIGS. 3A and 3B depict a logic flowchart of a method such as those depicted in FIGS. 1 and 2.

[0020] FIG. 4 depicts a logic flowchart of a method such as those depicted in FIGS. 1 and 2.

[0021] FIG. 5 depicts a logic flowchart of a device such as those depicted in FIGS. 1 and 2.

[0022] FIGS. 6A, 6B, and 6C depicts a logic flowchart of a method such as those depicted in FIGS. 1 and 2.

[0023] FIG. 7 depicts a logic flowchart of a device such as those depicted in FIGS. 1 and 2.

[0024] FIGS. 8A, 8B, 8C, and 8D depicts a logic flowchart of a method such as those depicted in FIGS. 1 and 2.

DETAILED DESCRIPTION

[0025] In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. The illustrative embodiments described in the detailed description, drawings, and claims are not meant to be limiting. Other embodiments may be utilized, and other changes may be made, without departing from the spirit or scope of the subject matter presented here.

[0026] The present application uses formal outline headings for clarity of presentation. However, it is to be understood that the outline headings are for presentation purposes, and that different types of subject matter may be discussed throughout the application (e.g., method(s) may be described under composition heading(s) and/or kit headings; and/or descriptions of single topics may span two or more topic headings). Hence, the use of the formal outline headings is not intended to be in any way limiting.

[0027] Methods, systems, and devices are described herein which include receiving data or providing data, wherein the data regards a physical condition affecting one or more subjects. The data regarding the physical condition may be acquired prior to the subject entering an environment where the physical condition exists. Methods, systems, and devices are described herein which include receiving data including data of a physical condition affecting one or more subjects. Methods, systems, and devices are described herein which include receiving data including data of a physical condition affecting one or more subjects. The methods, systems, and devices as described herein can further include sensing the physical condition affecting the one or more subjects. The physical condition affecting the one or more subjects includes, but is not limited to, an environmental condition, a signal from a global positioning device, a calendar entry, an environmental forecast, or a weather forecast, or a combination thereof. The physical condition may further include a physiological condition of the one or more subjects. A sensor may be located on the subject which detects the sensed physical condition. The sensor may be configured to monitor pH of the pulmonary tissue or pH of an exhalant in the subject. The sensor may be configured to monitor humidity of an exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, expiratory reserve volume, or residual volume.

[0028] The pharmaceutical composition includes at least one agent, e.g., at least one buffering agent, at least one basic agent, or at least one acidic agent, or a combination thereof, and is configured to achieve a selected pH range of the pulmonary tissue of the one or more subjects. The pharmaceutical composition may be administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject.
With reference to the figures, and with reference now to FIGS. 1 through 8, depicted is one aspect of a system that may serve as an illustrative embodiment of a method comprising receiving data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition is configured to contact pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects. A method for treating a pulmonary viral infectious disease in a subject comprising administering a pharmaceutical composition including at least one agent to a pulmonary tissue of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject, or a device comprising an aerosol generator and a pharmaceutical composition including a membrane selective for a charged ion configured to achieve a selected pH of a pulmonary tissue in a subject. Accordingly, the present application first describes certain specific exemplary methods of FIGS. 1 through 8; thereafter, the present application illustrates certain specific exemplary methods. Those having skill in the art will appreciate that the specific methods described herein are intended as merely illustrative of their more general counterparts.

Continuing to refer to FIG. 1, depicted is a partial diagrammatic view of an illustrative embodiment of a method for treating a pulmonary viral infectious disease in a subject or a device 110 for use with the method. In FIG. 1A, a method for treating a pulmonary viral infectious disease in a subject 100 includes administering a pharmaceutical composition 120 including at least one agent 130, 140 to a pulmonary tissue of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges 130, 140 configured to contact two or more levels 160, 170 of pulmonary tissue 150 of the subject. In FIG. 1B, the method includes administering a pharmaceutical composition 120 including at least one agent 130, 140 to a pulmonary tissue 150 of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges 130, 140, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels 160, 170 of pulmonary tissue 150 of the subject. The two or more distinct and non-overlapping particle size ranges 130, 140, may be configured to achieve a selected pH range in the two or more levels, for example, in the bronchus or bronchi 160 of the lungs, or further into the bronchial tree 170 towards the bronchi, bronchioles, alveolar duct, or alveoli of the lungs of the subject.

Continuing to refer to FIG. 2, FIG. 2A depicts a partial diagrammatic view of an illustrative embodiment of a method comprising receiving data 260 including data 270 of a physical condition affecting one or more subjects 200, the data 270 informing administration 215 of a pharmaceutical composition 220, 230, 240 in response to the physical condition, wherein the pharmaceutical composition is configured to contact pulmonary tissue 250, 280, 290 to treat a pulmonary disease or condition in the one or more subjects 200. The system or method may include a device 210. The system or method includes providing data 270 including data of a physical condition affecting one or more subjects, the data informing administration 215 of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition 220, 230, 240 contacts pulmonary tissue 250 to treat a pulmonary disease or condition in the one or more subjects. In FIGS. 2B and 2C, the pharmaceutical composition 220 includes at least one agent 230, 240 and is configured to achieve a selected pH range 280, 290 of the pulmonary tissue 250 of the one or more subjects 200. Two or more distinct and non-overlapping particle size ranges 230, 240, may be configured to achieve a selected pH range in the two or more levels, for example, in the bronchus or bronchi 280 of the lungs, or further into the bronchial tree 290 towards the bronchi, bronchioles, alveolar duct, or alveoli of the lungs of the subject.

FIGS. 3A and 3B depict a logic flowchart of a method such as those depicted in FIGS. 1 and 2. FIGS. 3A and 3B illustrate an exemplary method 300 for receiving data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition is configured to contact pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects.

FIG. 4 depicts a logic flowchart of a method such as those depicted in FIGS. 1 and 2. FIG. 4 illustrates an exemplary method 400 including providing data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition contacts pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects.

FIG. 5 depicts a logic flowchart of a device such as those depicted in FIGS. 1 and 2. FIG. 5 illustrates an exemplary device 500 including a signal-bearing medium which includes one or more instructions for receiving data including data of a physical condition affecting one or more subjects the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition contacts pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects.

FIGS. 6A, 6B, and 6C depict a logic flowchart of a method such as those depicted in FIGS. 1 and 2. FIGS. 6A, 6B, and 6C illustrate an exemplary method 600 for treating a pulmonary viral infectious disease in a subject which includes administering a pharmaceutical composition including at least one charged ion to a pulmonary tissue of the subject, wherein the pharmaceutical composition includes a membrane selective for the charged ion and is configured to achieve a selected pH of the pulmonary tissue in the subject.

FIG. 7 depicts a logic flowchart of a device such as those depicted in FIGS. 1 and 2. FIG. 7 illustrates an exemplary device 700 including an aerosol generator, and a pharmaceutical composition including a membrane selective for a charged ion configured to achieve a selected pH of a pulmonary tissue in a subject.

FIGS. 8A, 8B, 8C, and 8D depict a logic flowchart of a method such as those depicted in FIGS. 1 and 2. FIGS. 8A, 8B, 8C, and 8D illustrate an exemplary method 800 for treating a pulmonary viral infectious disease in a subject which includes administering a pharmaceutical composition including at least one agent to a pulmonary tissue of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pul-
monary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject.

Types of Data Regarding a Physical Condition or Environmental Condition

[0038] A method, system, or device is provided for receiving data including data of a physical condition affecting one or more subjects. The method, system, or device may sense one or more physical condition that is one or more environmental condition, signal from a global positioning device, calendar entry, environmental forecast, or weather forecast. An environmental condition may include, but is not limited to, air quality associated with smog, forest fire, volcanic ash; allergen conditions such as pollen count, mold spores, dander; weather conditions such as temperature, pressure, wind speed and humidity; and infection risk conditions.

[0039] The method, system, or device may further include a global positioning device to sense the current location of one or more subjects relative to the environmental condition. A calendar entry may be used to sense a current or future location of one or more subjects relative to the environmental condition. The calendar provides the date and time as well as scheduling information specific to a given subject or group of subjects regarding planned activities and or outings in the near and far future. An environmental forecast and or a weather forecast in combination with a calendar entry may predict a future environmental condition of one or more subjects. One or more subjects may communicate, provide, or receive information regarding current and future physical conditions for a given location and time. This information may be used to alert one or more subjects that they are currently in or will be entering in the future an environment with conditions that may increase the risk of contracting an infectious agent. In response to this information, one or more subjects may choose to self-administer a pharmaceutical composition that may prevent or mitigate the infection. Alternatively, the device may automatically deliver a pharmaceutical composition to one or more subjects based on the information regarding environmental conditions, location and time.

[0040] A number of environmental conditions associated with poor air quality may affect lung function or susceptibility to disease. For example, gases, particulates, and other chemicals associated with smog, forest fires and volcanic ash may contribute to poor air quality in a given location at a given time. As such information regarding current and projected environmental conditions related to air quality may be measured in a current location and or a future location and used to guide treatment of the lungs with the pharmaceutical composition.

[0041] The effects of smog on lung function and susceptibility to disease vary according to factors such as age, state of health, time of exposure, and dosage, but general symptoms include coughing, sneezing, headaches, tiredness, irritation, nausea, and hoarseness of the throat, nose, and eyes, and constrictions of the chest. In addition, nitrogen dioxide and ground-level ozone associated with smog may cause reductions in the immune system’s ability to fight viruses and bacteria in the respiratory system (see, e.g., Chauhan & Johnston BMB 68:95-112, 2003; Hollingsworth, et al., Proc. Am. Thorac. Soc. 4:240-246, 2007, which are incorporated herein by reference). In one aspect, exposure to nitrogen dioxide and ozone increases expression of intracellular adhesion molecule 1 (ICAM-1), an epithelial cell receptor for human rhinovirus. The gaseous and particulate components of smog may also damage the pulmonary epithelium. Nitrogen dioxide and ground-level ozone as well as sulfur dioxide may cause damage to the mucociliary clearance system or ciliary dyskinesia. The mucociliary clearance system plays a pivotal role in the protection of the respiratory tract against inhaled noxious agents such as airborne allergens, bacteria or viruses by trapping the agents in mucus and transporting the agents towards the pharynx and out of the lung by ciliary beating or coughing. As a result, the lung’s ability to resist disease is reduced, and illnesses, such as asthma, bronchitis and emphysema, may be aggravated.

[0042] Gases associated with smog including sulfur dioxide, ozone, nitrogen dioxide, total reduce sulfur compounds, and carbon monoxide may be measured using a number of methods, e.g., passive sampling methods, active sampling methods, automatic methods and remote methods. Passive sampling methods provide reliable, cost-effective air quality analysis and may provide a good indication of average pollution concentrations over a period of weeks or months. Passive samplers do not involve any pumping of air but instead rely on the natural flow of ambient air past the open end of a diffusion tube which contains two stainless steel gauzes placed at one end of a short cylinder. In the case of a nitrogen dioxide sampler, the steel gauze contains a coating of triethanolamine, which converts the nitrogen dioxide in the air to nitrite, the latter of which is trapped within the steel gauze and can be measured by laboratory analysis. Active sampling methods use physical or chemical methods to collect polluted air, and analysis is carried out later in the laboratory. Typically, a known volume of air is pumped through a collector, such as a filter or a chemical solution, for a set period of time. The collector is later removed for analysis. Samples can be collected daily, providing measurements for short time periods. Automatic methods produce high-resolution measurements of hourly pollutant concentrations or better, at a single point as measured using a variety of methods including spectroscopy and gas chromatography. Remote optical/long-path analyzers use spectroscopic techniques to make real-time measurements of the concentrations of a range of pollutants including nitrogen dioxide and sulfur dioxide. In one aspect, hydroperoxyl radicals, one of the most abundant free radicals in the atmosphere, may be measured using a chemiluminescence detection system as in U.S. Pat. No. 7,285,243, which is incorporated herein by reference.

[0043] In addition to noxious gases, smog may also contain particulate matter, e.g., black carbon. Black carbon is derived primarily from diesel exhaust and wood burning. These particles are small enough to penetrate and irritate the human pulmonary system. Black carbon is also able to adsorb other species such as air toxins. Black carbon may be measured using an air monitoring systems such as, for example, the Aethalometer™ (from, e.g., Magee Scientific, Inc. Berkeley, Calif.). The Aethalometer™ is a tape sampler that takes in air at a controlled rate and passes the air though a glass fiber filter. As the particulate matter accumulates on the filter, the device measures the attenuation of light at two channels. The black carbon channel is recorded at 880 nm and the UV channel is at 370 nm. Other devices for measuring air borne particulate matter include the nephelometer and the tapered element oscillating microbalance (TEOM).

[0044] Forest fires and other vegetation fires generate smoke which contributes to air pollution and may conse-
quently alter pulmonary function in a subject. Vegetative fire smoke consists primarily of water vapor, volatile organic compounds, semi-volatile organic compounds, particulate matter, and permanent gases. The gases found in forest fire smoke include CO, CO$_2$, NO$_2$, and ozone, similar to the contaminants associated with air pollution. Air quality monitoring may be done to intermittently or continuously measure key components of forest fire smoke. Air quality monitoring of CO, CO$_2$, and other permanent gases as well as particulates may be accomplished in the field using portable instruments. These may be hand-held, backpack, or o luggage carried; mobile labs or roving systems; and wearable instruments. For example, miniaturization of an ion mobility spectrometry system either "worn" or as part of a uniform, for example, may be used as an alarm device as well as for monitoring human exposure. Hand-held sensors may be used to measure CO, CO$_2$, and other permanent gases as well as particulate matter. Portable versions of photoionizing devices, gas chromatography-mass spectrometry, gas chromatography-ion mobility spectrometry, gas chromatography-gas chromatography, and ion mobility spectrometers may be used for monitoring volatile organic compounds. Depending upon distance from the flame front, the instruments may be defined as stand-off and point devices (near the flame front). The instruments may be defined as active or passive depending upon whether or not the sample is excited or not. And depending upon the height-level of the monitoring, the field methods can be classified as ground-based, aerial, or space (see, e.g., Stathopoulos & Goldammer, “Vegetation Fire Smoke: Nature, Impacts and Policies to Reduce Negative Influences on Humans and the Environment” presented at 4th International Wildland Fire Conference, Sevilla, Spain, May 13-17, 2007).

A volcanic eruption emits ash and gases into the atmosphere that can affect respiratory function. The potential respiratory symptoms in the subject from inhalation of volcanic ash include but are not limited to nasal irritation and discharge, throat irritation and sore throat, sometimes accompanied by dry coughing, severe bronchitis symptoms (hacking cough, production of sputum, wheezing, or shortness of breath) in individuals with pre-existing respiratory complaints, and airway irritation including shortness of breath, wheezing, and coughing in individuals with asthma or bronchitis. The severity of symptoms depends on a number of factors, including airborne concentration of total suspended particles, proportion of respirable particles in the ash (less than 10 $\mu$m), frequency and duration of exposure, presence of free crystalline silica and volcanic gases or aerosols mixed with the ash, meteorological conditions, and host factors (existing health conditions and the propensity of those exposed to incur respiratory problems), and the use of respiratory protective equipment. In addition, volcanic eruptions are the largest source of naturally occurring sulfur dioxide in the atmosphere.

Data from weather satellites may be used to identify volcanic plumes and to track their movement downwind. Explosive eruptions inject enormous volumes of volcanic ash and gases into the atmosphere, where the ash is carried downwind hundreds or thousands of miles and often remains airborne for days to weeks. As the ash and gas move and disperse downwind, it becomes increasingly difficult to distinguish an eruption cloud visually from weather clouds, especially at night or in poor weather. Sensors aboard geostationary and polar orbiting weather satellites record the amount of thermal energy in several different wavelengths emitted from weather and eruption clouds and the Earth’s surface. The image data from these different wavelengths may be used to detect and track an eruption cloud. Sulfur dioxide associated with volcanic eruptions may be measured from space using a satellite equipped with a total ozone mapping spectrometer.

An environmental condition may also include allergen conditions, e.g., pollen count, mold spores, and dander. Allergens such as pollen, mold, and dander may be another source of pulmonary irritation. In general, pollen is found mainly in the coarse fraction of airborne particles. Pollen in a given location may be measured by passing the ambient air through a filter which captures particulate matter, including pollen. The trapped pollen may be identified and quantified by counting the pollen spores under an optical microscope. Alternatively, pollen floating in air may be counted in real time using a pollen sensor that includes, for example, a light beam and a receiver for measuring the intensity of a light beam scattered by floating particles in a detection zone and a second receiver for measuring the intensity of a polarized light beam in a direction perpendicular to light illuminated by the light beam and means for measuring the degree of polarization of the particles for distinguishing pollen particles from other particles (U.S. Pat. No. 7,119,900, which is incorporated herein by reference).

In some aspects, allergen conditions may be inferred from the time of year in a given location. For example, the presence of pollen or other allergen may be inferred from the time of year in a given location. Pollen season begins earlier in warmer climates than in cooler climates and typically ends after the first hard freeze. Trees generally pollinate first followed by grasses and weeds. The time period over which a given pollen type is likely to be present may be dependent upon the geographical location. In one aspect, along the Northwest United States coast, the tree pollen season lasts from February to June, the grasses pollen season lasts from May to August, and the weeds pollen season lasts from May to September. In contrast, in the arid Southwest United States the tree pollen season lasts from February to June, the grasses pollen season lasts from April to October, and the weeds pollen season lasts from February to October.

Seasonal weather patterns influence the amount of pollen that plants produce in a growing season. In addition, daily weather conditions also have an effect on the amount of aggravating wind-dispersed pollen in the air. Blustery, windy days stir up pollen whereas windless and rainy days may lower pollen counts. Data regarding probable pollen in the atmosphere at a given time of year may be combined with data regarding the temperature, humidity and wind on a given day in a given location.

Other allergens such as mold spores as well as dander, including house mite, cockroach, cat, or dog allergens may also be found in the coarse fraction of airborne particles. Airborne mold spores may be measured by passing the ambient air through a filter which captures the mold spores. Material trapped by the filter may be examined by optical microscopy. In some aspects, the filter itself may be washed or dissolved in a sterile aqueous solution and mold released into the solution may be cultured on an agar plate or in a liquid broth to identify which if any mold strains are in the sampled air.

An environmental condition may also include weather conditions, e.g., temperature, humidity, wind speed, and air pressure. A number of weather related physical conditions that may affect lung function or susceptibility to dis-
ease may be measured including but not limited to temperature and humidity. Temperature may be simply measured using a thermometer. Humidity is normally measured as relative humidity and may be measured using a hygrometer. Temperature and humidity are closely linked. Relative humidity is the percentage of moisture in the air relative to the maximum amount the air can hold at a given temperature. When air at a given temperature contains all the water vapor it can hold at that temperature, it has a relative humidity of 100 percent. If the humidity exceeds 100 percent, moisture will begin to condense from the air. Warm air can hold more moisture than cool air, so that the relative humidity of a sample of air will change as the temperature changes, even though the actual amount of moisture in the sample air does not. As a sample of air cools the relative humidity rises.

[0052] The condition of a potentially infectious environment may be directly measured by assessing the presence or absence of airborne pathogens. Airborne pathogens, e.g., viral particles, may be detected by recovering the particles in or on a collection medium (liquid, semisolid, or solid substrate), and then assaying the substrate for the presence of the targeted virus using an appropriate assay system. Airborne viral particles may be collected using an impinger in which a converged stream of environmental air is directed onto a liquid collection medium (see, e.g., Hermann, et al., Appl. Environ. Microbiol. 72:4811-4818, 2006, which is incorporated herein by reference). Capture mediums include, but are not limited to, filters, bubblers, or impactors. Real time polymerase chain reaction (RT-PCR) amplification may be used to detect and identify viral pathogens. Methods are provided for using RT-PCR to detect and identify the avian H5N1 influenza virus (Chen et al., J. Med. Microbiol. 56:603-607, 2007, which is incorporated herein by reference). Similarly, airborne rhinovirus may be collected on Teflon membranes and identified and quantified by PCR (see, e.g., Myatt, et al., BMC Public Health 3:5, 2003, which is incorporated herein by reference). Alternatively, airborne pathogens may be detected using some form of microsensor. For example, arrays of silicon cantilever beams as microresonator sensors are provided to detect individual virus particles (see, e.g., Gupta, et al., Applied Physics Lett. 84: 1976-1978, 2003, which is incorporated herein by reference).

[0053] Alternatively, an infection risk condition may be implied from the time of year and global location. For example, "flu" season or that portion of the year in which there are regular outbreaks of influenza infections usually occurs in the cold half of the year in each hemisphere. In the United States, flu season may run from November through March of the following year. During the colder portion of the year, people remain indoors more often and as such are in closer contact, allowing for easier viral transmission. In addition, cold temperatures lead to drier air and may dehydrate mucus and as such prevent the body from effectively expelling virus particles. The virus itself may survive longer on surfaces in cold temperatures.

[0054] Alternatively, an infection risk condition may be communicated to a subject or group of subjects from an agency tracking viral infection in a given location. Such an agency might be, for example, a local Public Health authority, the Center for Disease Control (CDC), the World Health Organization (WHO) or similar agencies in a given location. The location may be the current location of the subject or group of subjects. Alternatively, the location may be the location to which the subject or group of subjects will be traveling to in the near future. The CDC provides weekly influenza surveillance data broken down by region such as Northeast versus Pacific.

[0055] Data regarding environmental conditions may be communicated, provided, or received from any of a number of sensors including but not limited to sensors implanted in a subject or group of subjects, sensors carried or worn by a subject or group of subjects, sensors present in a room(s) and or building(s) frequented by a subject or group of subjects, public spaces frequented by a subject or group of subjects, remote sensors in distance locations and or associated with satellites, or combinations thereof. Information communicated, provided, or received from the sensors is communicated to a subject or group of subjects.

[0056] Data regarding environmental conditions may be collected by a sensor that is incorporated into the subject. For example, a miniaturized sensor may be implanted or inserted into a part of the respiratory tract such as, for example, a nostril, a sinus, a tooth, back of the throat, or other part of the respiratory system over which air normally flows. Alternatively, the miniaturized sensor may be implanted or inserted on other parts of the body. Device may include a micromechanical sensor that enables measurement of pressure, a temperature, an air mass, an air quality, a dew point, a humidity of a gas, a chemical composition of a gas or of a liquid, for example (see, e.g., U.S. Pat. No. 7,213,465, which is incorporated herein by reference).

[0057] Data regarding environmental conditions may be communicated, provided, or received from a sensor that is carried by the subject or group of subjects. For example, the sensor may be incorporated into everyday devices normally carried by a subject or group of subjects. Examples include but are not limited to a cell phone, a pager, a PDA, blackberry, or other. For example, Sakharpa describes a mobile telecommunications handset with an air pollution meter (U.S. Patent Application 2008/0045156 A1, which is incorporated herein by reference). Alternatively, the device may be worn by the subject. Examples include, but are not limited to, a sensor device worn directly over the mouth and or nose, a sensor device worn on the back or around the waist or neck, a sensor device incorporated into a piece of jewelry such as a necklace, bracelet, wrist watch, and the like, or a sensor device incorporated into an article of clothing.

[0058] Data regarding environmental conditions may be communicated, provided, or received from a sensor that is situated in a private or public room or building or open space frequented by a subject or group of subjects such as, for example, a home, office, classroom, shopping mall, or other public space. The sensor may be incorporated into a stand-alone device that sits on a desk, is mounted on the wall, or stands on the floor. Alternatively, the sensor may be incorporated into an air flow system associated with a room or building or public space. A sub-assembly device is provided for detecting and reporting on allergen data within a room or building in which the device is located (U.S. Pat. No. RE39, 871, which is incorporated herein by reference). Information from the sensor may be sent wirelessly to the subject or group of subjects.

[0059] Data regarding environmental conditions may be communicated, provided, or received from a remote sensor and sent either directly or indirectly to a subject of group of subjects. For example, information regarding an environmental condition such as air quality, for example, may be received wirelessly by a subject or group of subjects from one or more
mobile measuring units with global positioning information (see, e.g., U.S. Patent Application 2008/0024323 A1, which is incorporated herein by reference). Alternatively, information regarding environmental and/or weather conditions may be communicated, provided, or received indirectly from any of a number of collecting agencies. Agencies which collect information regarding environmental conditions include, but are not limited to, local, national and/or international weather services, e.g., the National Oceanic and Atmospheric Administration (NOAA) and the National Weather Service; local, national and/or international fire monitoring agencies such as, for example, the United States Forest Service (USFS) and Global Forest Information Service (GFIS); local, national and/or international volcano monitoring agencies such as, for example, United States Geological Survey (USGS). Information regarding weather conditions and air quality may be provided by a service that accumulates such information for one or more locations and transmits the information to a subject or group of subjects to a device such as a computer, a PDA, a cellular telephone, a pager, a dedicated display device or a public display (U.S. Pat. No. 7,181,345, which is incorporated herein by reference). Other sources of information include, but are not limited to, the internet, television and radio stations, public health departments, allergy clinics, and the like.

Type of Data Regarding a Physical Condition—Physiological Condition

A method, system, or device is provided for receiving data including data of a physical condition affecting one or more subjects. The method, system, or device may further sense one or more physical conditions which include one or more physiological condition of a subject or group of subjects. The physiological condition may be the pH of the pulmonary tissue of a subject or group of subjects. The physiological condition may further be one or more of the humidity of exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, expiratory reserve volume, or residual volume of a subject or group of subjects.

The method, system, or device includes one or more sensors configured to monitor at least one of the pH of the pulmonary tissue in the subject or pH of an exhalant in the subject. The one or more monitoring sensor may be part of a handheld device. The one or more sensor may be associated with a mask worn over the mouth and/or nose of the subject. In some aspects, the one or more monitoring sensor may be miniaturized and temporarily or permanently incorporated into an airway passage of the subject. The one or more monitoring sensor may be incorporated into the upper respiratory tract, including, but are not limited to, the nasal cavity, pharynx and/or larynx. Data generated by the one or more monitoring sensor may be sent wirelessly to a device associated with the subject and/or to a device associated with a third party, e.g., a physician or other caregiver.

The pH of pulmonary tissue in a subject may be measured in exhaled breath of the subject. For example, pH may be monitored in expired breath condensate (EBC). EBC consists of: (1) aerosolized particles of airway lining fluid evolved from the airway wall by turbulent airflow, that serves as seeds for substantial; and (2) water vapor condensation, which then serves to trap (3) water soluble volatile gases. The normal range of pH values of fluid lining human airways ranges from pH 6.5 to pH 7.5 (see, e.g., Tanaka, et al., Eur. Respir. J. 11:1301-1306, 1998, which is incorporated herein by reference). Sampling may be accomplished by having a subject breathe at tidal volumes orally into a mouthpiece attached to a cold condenser (RTube, Respiratory Research Inc., Austin, Tex.; ECoScreen II, VIASYS Healthcare, Yorba Linda, Calif.). In this instance, pH may be assayed after Argon derivation of the EBC. In addition to oral collection methods, EBC may be collected through a nasal cannula and/or an endotracheal tube. Collection times may be as short as 90 seconds or over an hour to obtain sufficient EBC. Ten minutes of breathing is commonly employed. Alternatively, pulmonary pH of a subject may be monitored in real time using a miniaturized self-condensing pH sensor as described by Tsukashima, et al., in U.S. Patent Application 2007/0068810 A1, which is incorporated herein by reference.

In some instances, the pH of expired breath condensate (EBC) may be monitored by a microsensor using a pH sensitive ion-sensitive effect transistor (ISFET). In this instance, a metal oxide such as SiO$_2$, Ta$_2$O$_5$, and/or Al$_2$O$_3$, for example, may donate or accept a proton from the solution (in this instance the breath condensate) and leave a negatively charged or a positively charged surface group, respectively, thus generating a surface potential that varies depending upon the pH of the solution (see, e.g., U.S. Pat. Nos. 6,132,893 and 6,464,940, which are incorporated herein by reference).

The sensor as provided in the method, system, or device for monitoring the pH in the expired breath condensate of the subject may be sufficiently small to be semi-permanently or permanently located in a segment of the airway of a subject. The sensor may be incorporated into the upper respiratory tract, including, but not limited to, the nasal cavity, pharynx and/or larynx. Alternatively, the sensor may be incorporated into a dental or nasal prosthesis (see, e.g., U.S. Patent Application 2007/0106138 A1, which is incorporated herein by reference) or into a piece of jewelry such as, for example, a nose or tongue piercing (see, e.g., U.S. Patent Application 2005/0209526 A1, which is incorporated herein by reference).

Alternatively, the sensor for monitoring the pH in the expired breath condensate of the subject may be incorporated into a mask or other covering of the mouth and/or nose that is worn by the subject (see, e.g., U.S. Patent Application 2007/0068810 A1, which is incorporated herein by reference). In some instances, the mask may be worn at all times, and as such may continuously and in real time measure the pH of the expired breath condensate of a subject. Alternatively, the mask may be worn temporarily to measure the pH of the expired breath condensate of a subject at any given point in time.

The method, system, or device as provided herein may further include a sensor configured to monitor other physiological conditions of a subject such as, pH of the pulmonary tissue or pH of an exhalant of a subject. The sensor may be configured to monitor further conditions which include, but are not limited to, humidity of an exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, expiratory reserve volume, or residual volume.

Effects of Pulmonary pH and Pharmaceutical Composition on Viral Infection in a Subject

A method, system, or device is provided for receiving data including data of a physical condition affecting one or more subjects. The pH within the respiratory system,
whether acidic, neutral or basic, may contribute to susceptibility to viral infection in terms of both target cell invasion, replication within the target cell, and release from the target cell. A low pH environment in endocytic and exocytic compartments of a target cell has been shown to be a prerequisite for translocation of a viral particle into the cell cytoplasm. Two examples of viruses that infect the pulmonary tissue and may be influenced by pH include the influenza viruses, associated with flu epidemics, and human rhinoviruses, associated with the common cold. A number of other viruses induce infection within the respiratory system and may be influenced by the pH of the pulmonary tissue. Viruses infectious to the respiratory system include, but are not limited to, parainfluenza virus, coronavirus, respiratory syncytial virus, adenovirus, cytomegalovirus, and hantavirus.

In general, three steps determine the early events in viral infection of a host cell including adsorption to the plasma membrane by binding to specific receptors, penetration, and subsequent uncoating of the genome. Many enveloped and nonenveloped viruses enter a cell via receptor-mediated endocytosis, with membrane penetration and uncoating taking place from the endosomes. Internalization of viral particles is initiated by invagination of the plasma membrane. After pinching off, these vesicles derived from the plasma membrane reach the early endosome compartment. In early endosomes, the internalized material are either sorted into the recycling pathway or directed via late endosomes to lysosomes for degradation. Viruses are transported to the compartment providing conditions suitable for delivery to the cytoplasm. The low pH environment, e.g., pH 5.0 to 6.5, in endocytic and exocytic compartments has been shown to be a prerequisite for translocation into the cytoplasm.

Influenza virus is an enveloped negative-sense RNA virus. It is major public health problem worldwide and is responsible for 20,000 deaths annually in the United States alone, with the frequent emergence of new and potentially deadly strains of the virus. As with all viruses, influenza virus needs to penetrate target cells to cause infection. An important component of influenza infectivity is the virally-associated surface glycoprotein hemagglutinin which plays a role in recognition and binding of the virus to host cells as well as fusion of the virus with the host cell membrane. Hemagglutinin consists of a receptor-binding (HA1) domain and a membrane-anchoring (HA2) domain linked by a disulfide bond. Hemagglutinin selectively binds to α2,6-sialosides on glycoproteins and glycolipids associated with the outer surface of the target cells. Different viral hemagglutinins preferentially recognize different sialic acid-galactose linkages. For example, human influenza hemagglutinin preferentially binds α2,6 linkages to galactose while the avian H5N1 influenza hemagglutinin, for example, prefers α2,3 linkages to galactose. The human lung and airway epithelial cells, a prime target for influenza infection, have an abundance of α2,6 linkages. The ability of hemagglutinin to bind to sialylated cell surface receptors may be pH dependent.

The influenza viral particles bound to the target cells through the interaction of hemagglutinin with sialylated cell surface receptors are taken up by the target cell through the process of endocytosis. The low pH environment of the endosomes induces a large conformational change in hemagglutinin which in turn is thought to trigger fusion between the viral and the endosomal membranes. The optimal pH range for membrane fusion by hemagglutinin is between 5 and 5.5. The low pH environment of the endosome also activates the influenza virus M2 protein ion channel which begins to conduct protons across the viral membrane. The lowered internal virion pH is thought to weaken protein-protein interactions between the viral matrix protein (M1) and the ribonucleoprotein (RNP) core. Preventing the release of M1 protein results in incomplete viral uncoating and attenuated viral replication (see, e.g., Takeda et al., J Virol. 76:1391–1399, 2002, which is incorporated herein by reference). As such, modulating the pH within the pulmonary tissue may influence influenza infectivity (see, e.g., U.S. Patent Application 2008/000473 A1, which is incorporated herein by reference).

In some instances, lowering the pH of the pulmonary tissue with one or more acidic agents may prevent hemagglutinin and consequently the influenza virus from binding to the target cells in the first place. It is conceivable that premature exposure of virus to low pH in the extracellular environment might induce conformational changes to glycoproteins spike on the virus surface, thereby interfering with initial binding to the target host cell (see, e.g., Rennie et al., Respir. Res. 8:38, 2007, which is incorporated herein by reference).

Human rhinoviruses, the most frequent cause of upper respiratory tract infections known as “the common cold”, may be inactivated by acidic solutions or below pH 5.3 (see, e.g., Kurth, et al., Antimicrob. Agents Chemother. 26:924-927, which is incorporated herein by reference). Inactivation of rhinoviruses by low pH is thought to be due to conformational changes in capsid proteins at pH values of less than 6.2, leading to loss of the VP4 subunit of the capsid and rendering the virus noninfectious. Treatment of mammmalian cells infected with rhinovirus with acidic solutions such as, for example, citrate/phosphate buffer (pH 5.0), ascorbate (pH 5.0), or phthalate (pH 5.0), reduce viral titer by as much as 90% (see, e.g., Gem, et al., J. Infect. Dis. 195:1137-1143, 2007, which is incorporated herein by reference).

Influenza viruses may also be inactivated by low pH. For example, Influenza A Sydney/5/93 [H3N2], Influenza A Hong Kong/8/68 [H3N2] and avian reassortment virus A/Washington/2/95/80 X A Mallard/New York/6750/78 [H3N2] are rapidly inactivated in vitro by contact with acid buffered solutions at pH 3.5 (see, e.g., Rennie et al., Respir. Res. 8:38, 2007, which is incorporated herein by reference).

As such, modifying the pH of the pulmonary tissue with a pharmaceutical composition configured to deliver a pH modifying agent may prevent and/or treat a viral infection by preventing binding, fusion, and replication of the viral particles. Administration of the pharmaceutical composition may be informed by sensing the pH of the pulmonary tissue of a subject.

Pharmaceutical Compositions and Particle Size

In some aspects of the methods, systems, or devices provided herein, it may be beneficial to alter the pH, e.g., lower or raise the pH, in one level of the pulmonary tree while maintaining the pH in another level of the pulmonary tissue. Directing the pharmaceutical composition to one or more levels of the pulmonary tissue may be accomplished by varying the particle size of the one or more agents of the pharmaceutical composition. This may be dictated by where in the pulmonary tissue a particular viral infection is likely to occur. For example, human rhinoviruses commonly infect epithelial cells in the upper respiratory tract (see, e.g., Whitteman, et al., J. Biol. Chem. 278:11954-11961, 2003, which is incorporated
herein by reference). As such, the pharmaceutical composition may be directed specifically to the upper respiratory tract, for example, for the prevention and treatment of human rhinovirus. In some instances, similar viral strains may target host cells in different locations within the respiratory tract (see, e.g., Uiprasertkul, et al., Emerging Infectious Dis. 11: 1036-1041, 2005; Matrosovich, et al., PNAS 101: 4620-4624, 2004, which are incorporated herein by reference). For example, human influenza A specifically targets epithelial cells in the upper respiratory tract that express the 2,6-linked sialyl-galactosyl moieties. In contrast, avian influenza (H5N1) targets epithelial cells expressing the 2,3-linked sialyl-galactosyl moieties. These cells in humans are primarily located deep in the lower respiratory tract in ciliated epithelial cells and Type II pneumocytes. The pharmaceutical composition may be selectively directed to a level or levels of the pulmonary tissue based on the potential viral infection site, the latter of which is dependent upon which virus a subject has been exposed to or may be exposed to in the future. Directing the pharmaceutical composition to one or more levels of the pulmonary tissue may be accomplished by varying the particle size of the one or more agents of the pharmaceutical composition.

The pharmaceutical composition may be administered as two or more particle sizes of the same or different pH modifying agent for delivery to different levels of the pulmonary tissue. The two or more particle sizes may range from approximately 1 to 4 μm, approximately 5 to 10 μm, approximately 15 to 40 μm, or approximately 50 to 100 μm. The two or more particle sizes may range from approximately less than about 10 μm, less than about 6 μm, less than 4 μm, less than 2 μm, or less than about 1 μm. The particle size of a pharmaceutical composition is an important variable in defining the dose deposited and the distribution of the pharmaceutical composition in the pulmonary tissue (see, e.g., Labiris & Dolovich, Br. J. Clin. Pharmacol. 56:588-599, 2003, which is incorporated herein by reference). Fine particles more readily distribute in the peripheral airways while larger particles may deposit in the central airways or upper respiratory tract. A particle size may be defined by its mass median aerodynamic diameter (MMAD). Particles may be deposited by inertial impaction, gravitational sedimentation or diffusion depending upon their size. While deposition occurs throughout the airways, inertial impaction generally occurs in the first 10 generations of the lung where the air velocity is high and flow is turbulent. Deposition by gravitational sedimentation predominates in the last five to six generations of the airways (smaller bronchi and bronchioles) where air velocity is low. In the alveoli region, air velocity is negligible and as such particles are deposited by sedimentation and diffusion. Those particles not deposited during inhalation are exhaled.

In general, larger particles do not readily follow changes in air flow direction and tend to deposit by inertial impaction in the upper respiratory tract. For example, most particles greater than 10 μm are deposited in the oropharyngeal region with a large amount impacting on the larynx. Aerosols with MMAD of 5-10μm are mainly deposited in the large conducting airways as well as in the oropharyngeal region. Intermediate sized particles (3-5 μm) are carried further into the small airways of the bronch and bronchioles, with 50% of 3 μm particles reaching the alveolar region. Particles that are less than 3 μm may behave more like gas molecules following the airflow all the way to the alveoli. However, very small particles of less the 0.5 μm, for example, may fail to be deposited in the alveoli and instead may be exhaled.

Deposition of a pharmaceutical composition in the lungs may also be controlled by the inspiratory flow rate, the tidal volume and respiratory frequency of the subject (see, e.g., Labiris. Br. J. Clin. Pharmacol. 56:600-612, 2003, which is incorporated herein by reference). Controlling the air velocity or inspiratory flow rate by slow inhalation will maximize the number of particles that reach the alveoli and minimize the number that are exhaled. For example, fast inhalations may result in reduced peripheral deposition because the aerosol is more readily deposited by inertial impaction in the conducting airway and oropharyngeal region. When aerosols are inhaled slowly, deposition by gravitational sedimentation in peripheral region is enhanced. Peripheral deposition may also be increased with an increased in tidal volume and a decrease in respiratory frequency. As such, holding one’s breath after inhalation may enable better penetration of composition into periphery of lungs.

The particle size and deposition depth of the pharmaceutical composition entering the lungs is a function of the inhaler device used and the composition of the pharmaceutical composition. Inhalers and nebulizers of different types each have the ability to generate aerosol particles of a certain size range. For liquid formulations containing soluble pharmaceutical compositions, the size of the aerosol particle is largely a function of the design and operation of the delivery device such as the nebulizer or "atomizer" that converts the liquid into a vapor or mist. For pharmaceutical compositions in powder form and for insoluble pharmaceutical compositions that are suspended or dispersed in emulsions, the particle size in the formulation of the pharmaceutical composition is an important determining factor.

The particle size and deposition depth of the pharmaceutical composition entering the lungs is a function of the formulation of the pharmaceutical composition. Ideally the formulation retains the activity of the pharmaceutical composition as well as efficiently delivers the composition to the appropriate site of action within the lungs and allows the composition to remain in the lungs long enough to have the desired pharmacological effect. Formulating a pharmaceutical composition as a dry powder for inhalation may involve, e.g., either micronization via jet milling, precipitation, freeze-drying or spray-drying using various excipients, such as lipids and polymers, or carrier systems, such as lactose or other sugars. Particles of different sizes may be generated by modifications to the methods described above.

The size of one or more particles of the pharmaceutical composition may be measured using any of an number of methods including, but not limited to, light scattering, x-ray sedimentation, electrical sensing using the Coulter principle, sieves, spectroscopy, and microscopy combined with image analysis. In one aspect, microscopy, e.g., optical microscopy, scanning electron microscopy, laser scanning microscopy, confocal microscopy or scanning probe microscopy may be combined with image analysis software to determine the size and shape of particles (see, e.g., U.S. Pat. No. 7,009,169, which is incorporated herein by reference). The Clemex Particle Size Analyzer—PS3 is an example of a commercially available instrument for measuring particle size and shape using microscopy and image analysis (from Clemex Technologies, Inc., Longueuil, Canada). Another common method
for particle size determination is to use a light scattering instrument which measures the average particle size of a population of particles as well as the distribution of the particle size of the particles. When light strikes a particle, scattering (diffraction) occurs. The light scatters in all directions, but for larger particles there is relatively more scattering to the front while for smaller particles there is relatively more scattering to the sides and back. The light scattering method reports a three-dimensional (i.e., volume) equivalent sphere diameter. One example of a commonly used light scattering instrument is the Horiba LA-920 laser light diffraction instrument (from Horiba Instruments, Inc., Irvine, Calif.). The light scattering method is particularly adapted to measuring particle size and particle size distributions of the small particles in a dispersion.

One or more particles may be sized to generate a monodisperse population of particles. Particles that are dry powder polydisperse powder particles, for example, may be sized using a series of individual and or nested sieves that may further contain beads, disks and/or other non-geometric shapes that are rotated, vibrated or agitation in any of a number of directions to generate monodisperse particles (see, e.g., U.S. Pat. No. 6,207,310, and U.S. Pat. No. 6,197,835 which are incorporated herein by reference). The monodisperse population may be characterized using the particle size analysis methods described above.

Therapeutic Pharmaceutical Compositions

The method, system, or device as provided herein may communicate, provide, or receive data on the environmental and/or physiological conditions and send the data to the one or more subjects, or to a third party, for example, a physician or other caregiver, or to a combination thereof. Upon receiving information regarding the environmental and/or physiological condition, a pharmaceutical composition or dosage form may be administrated to the pulmonary tissue of the subject in response to a current condition. Alternatively, a pharmaceutical composition may be administrated to the pulmonary tissue of the subject as a prophylactic prior to traveling to a different location for which information has been communicated, provided, or received regarding a current or an anticipated environmental condition. A pharmaceutical composition may be, e.g., a basic agent, an acidic agent, or a buffering agent to modify pulmonary pH; an antiviral agent to treat viral pulmonary disease; or an antihistamine or decongestant to treat viral or bacterial pulmonary disease or allergy.

Methods and compositions are provided wherein the pharmaceutical composition may be one or more agents that may be used to adjust the pH within the pulmonary tract of the subject. The pharmaceutical composition may include at least one agent to a pulmonary tissue of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject. The one or more pharmaceutical agents may be one or more of a basic agent, an acidic agent, a buffering agent, or some combination thereof. The pharmaceutical composition may be one or more basic agent comprising a proton acceptor for raising the pH in the airways such as, for example, ammonia or bicarbonate. Alternatively, the pharmaceutical composition may be one or more acidic agent comprising a proton donor for lowering the pH in the airways such as, for example, acetic acid, succinic acid, or dilute hydrochloric acid, or other proton donors. The pharmaceutical composition may include one or more buffering agents, including, but not limited to, sodium bicarbonate, potassium bicarbonate, phosphate buffer, citrate buffer, lactate buffer, pyruvate buffer, phthalalate buffer, glycine (amino acetic acid), bicine (N,N-bis(2-hydroxyethyl)glycine), tricine-[N-(tris(hydroxymethyl)methyl]glycine), CAPS (3-(cyclohexamino)-1-propanesulphonic acid, CAPSO (3-(cyclohexamino)-2-hydroxypropanesulfonic acid), 2-(cyclohexamino)-ethanesulphonic acid, BIS-TRIS propane, MOPS, HEPES, DIPSO, TAPSO, TRIZMA, HEPPSO, POPSO, EPPS, dibasic sodium phosphate, dibasic potassium phosphate, or triethanolamine.

In some instances, the pharmaceutical composition may include one or more agents used for treating a viral infection. Examples of agents used for treating influenza, for example, include, but are not limited to, neuraminidase antagonists as exemplified by zanamivir and oseltamivir and M2 viral channel antagonists as exemplified by amantadine and rimantadine. Other antiviral drugs of the pharmaceutical composition may include, but not limited to, acyclovir, valacyclovir, famciclovir, penciclovir, trifluridine, ganciclovir, valganciclovir, cidofovir, abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine, delavirdine, efavirenz, nevirapine, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, interferon alfa, adefovir dipivoxil, entecavir, and ribavirin.

In some instances, the pharmaceutical composition may further include one or more agent used for treating a bacterial infection. Examples of agents used for treating bacterial infections include but are not limited to, beta-lactam compounds such as penicillin, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, ampicillin, ticarcillin, amoxicillin, carbenicillin, and piperacillin; cephalosporins and cephamycins such as cefadroxil, cefazolin, cephalexin, cefalothin, cephapirin, cephradine, ceficlador, cefamandole, cefonicid, cefuroxime, cefprozil, loracarbef, ceforanide, cefoxitin, cefmuzate, cefotetan, cefoperazone, cefotaxime, cefazidime, cefoxime, ceftriaxone, cefixime, cepodoxime, proxetil, cefdinir, cefditoren, pivoxil, cefibuten, moxaclactam, and cefepime; other beta-lactam drugs such as aztreonam, clavulanic acid, sulbactam, tazobactam, ertapenem, imipenem, and meropenem; other cell wall membrane active agents such as vancomycin, teicoplanin, daptomycin, fosfomycin, bacitracin, and cycloserine; tetracyclines such as tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, doxycycline, minocycline, and tigecycline; macrolides such as erythromycin, clarithromycin, azithromycin, and telithromycin; aminoglycosides such as streptomycin, neomycin, kanamycin, amikacin, gentamicin, tobramycin, sisomicin, and netilmicin; sulfonamides such as sulfacycline, sulfisoxazole, sulfamethizole, sulfadiazone, sulfamethoxazole, sulphonyluride, and sulfadoxine; fluoroquinolones such as ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, and ofloxacin; antimycobacteria drugs such as isoniazid, rifampin, rifabutin, rifampentine, pyrazinamide, ethambutol, ethionamide, capreomycin, clofazimine, and dapson; and miscellaneous antimicrobials such as colistimethate sodium, methenamine hippurate, methenamine mandelate, metronidazole, mupirocin, nitrofurantoin, polymyxin B, clindamy-
cin, choranphenicol, quinupristin-dalfopristin, linezolid, spectinomycin, trimethoprim, pyrimethamine, and trimetho-
prim-sulfamethoxazole.

In some instances, the pharmaceutical composition may include one or more agents used for treating the symp-
toms of a viral or bacterial infection or treating in response to an allergen. The pharmaceutical composition may include one or more decongestants, including, but are not limited, oxymetazoline, phenylephrine, xylometazoline, or pseudo-
ephedrine. The pharmaceutical composition may also include an expectorant, e.g., guaifenesin. The pharmaceutical composition may further include an antihistamine, including, but are not limited, carboxinamine, dimenhydrinate, diphen-
hydramine, tripeledennine, hydroxyzine, cyclobenzaprine, mecliz-
ine, brompheniramine, chlorpheniramine, promethazine, cypres-
hetadine, fexofenadine, loratadine, or cetirizine.

Formulation of Pharmaceutical Compositions

Liquid Aerosol

The pharmaceutical composition may be formulated for inhalation administration as a liquid aerosol. In this instance, the one or more agent, e.g., one or more acidic, basic or buffering agent, may be dissolved into an appropriate solvent. Examples of appropriate solvents for inhalation include, but are not limited to water, alcohols, propylene glycol.

Dry Powder

The pharmaceutical composition including at least one agent to a pulmonary tissue of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject may be formulated for inhalation administration as a dry powder. Formulating the pharmaceutical composition as a dry powder for inhalation may involve particle size reduc-
tion using jet milling, controlled precipitation, sieving, freeze-drying or spray-drying, for example. The pharmaceut-
ical composition may be formulated in the absence of added excipients. Alternatively, the pharmaceutical composition may be formulated with added excipients. Examples of possible excipients for dry powder formulation for inhalation include, but are not limited to, lactose, dextran, mannitol, glucose, or a combination thereof. The pharmaceutical composition may also include surfactants such as oleic acid.

Liposomes

In another aspect, the pharmaceutical composition including at least one agent to a pulmonary tissue of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject may be formulated for inhalation as part of a liposome. Dried phospholipids placed into an aqueous environment will spontaneously associate into multilamellar structures that function as permeability barriers. These lipid vesicles, termed liposomes, are composed of aqueous compartments separated from each other and the external medium by a series of closed concentric lipid bilayers. The composition of the aqueous compartments is the same as the medium in which the liposomes were formed; thus making it possible to entrap a wide variety of materials within the lipid bilayers.

The liposomes of the pharmaceutical composition as provided herein may be comprised of one or more of a variety of lipids. Suitable lipids include amphipathic lipids in which the hydrophobic portion of the lipid material orients into a hydrophobic phase, while the hydrophilic portion orients toward the aqueous phase. Such compounds include, but are not limited to, phospholipids, aminolipids, and sphingolipids. Representative phospholipids include sphingomy-
elin, phosphatidylethanolamine, phosphatidylcholine, phosphatidylycerine, phosphatidylcholine, phosphatidylglycerol, palm itoyloylethanolamine, l-ceramide, ceramide, sphingosine, or sphingosine 1-phosphate. Suitable lipids include amphipathic lipids in which the hydrophobic portion of the lipid material orients into a hydrophobic phase, while the hydrophilic portion orients toward the aqueous phase. Such compounds include, but are not limited to, phospholipids, aminolipids, and sphingolipids. Representative phospholipids include sphingomyelin, phosphatidylethanolamine, phosphatidylcholine, phosphatidyserine, phosphatidylcholine, phosphatidylglycerol, palm itoyloylethanolamine, l-ceramide, ceramide, sphingosine, or sphingosine 1-phosphate. Suitable lipids include amphipathic lipids in which the hydrophobic portion of the lipid material orients into a hydrophobic phase, while the hydrophilic portion orients toward the aqueous phase. Such compounds include, but are not limited to, phospholipids, aminolipids, and sphingolipids. Representative phospholipids include sphingomyelin, phosphatidylethanolamine, phosphatidylcholine, phosphatidyserine, phosphatidylcholine, phosphatidylglycerol, palm itoyloylethanolamine, l-ceramide, ceramide, sphingosine, or sphingosine 1-phosphate. Suitable lipids include amphipathic lipids in which the hydrophobic portion of the lipid material orients into a hydrophobic phase, while the hydrophilic portion orients toward the aqueous phase. Such compounds include, but are not limited to, phospholipids, aminolipids, and sphingolipids. Representative phospholipids include sphingomyelin, phosphatidylethanolamine, phosphatidylcholine, phosphatidyserine, phosphatidylcholine, phosphatidylglycerol, palm itoyloylethanolamine, l-ceramide, ceramide, sphingosine, or sphingosine 1-phosphate. Suitable lipids include amphipathic lipids in which the hydrophobic portion of the lipid material orients into a hydrophobic phase, while the hydrophilic portion orients toward the aqueous phase. Such compounds include, but are not limited to, phospholipids, aminolipids, and sphingolipids. Representative phospholipids include sphingomyelin, phosphatidylethanolamine, phosphatidylcholine, phosphatidyserine, phosphatidylcholine, phosphatidylglycerol, palm itoyloylethanolamine, l-ceramide, ceramide, sphingosine, or sphingosine 1-phosphate. Suitable lipids include amphipathic lipids in which the hydrophobic portion of the lipid material orients into a hydrophobic phase, while the hydrophilic portion orients toward the aqueous phase. Such compounds include, but are not limited to, phospholipids, aminolipids, and sphingolipids. Representative phospholipids include sphingomyelin, phosphatidylethanolamine, phosphatidylcholine, phosphatidyserine, phosphatidylcholine, phosphatidylglycerol, palm itoyloylethanolamine, l-ceramide, ceramide, sphingosine, or sphingosine 1-phosphate. Suitable lipids include amphipathic lipids in which the hydrophobic portion of the lipid material orients into a hydrophobic phase, while the hydrophilic portion orients toward the aqueous phase. Such compounds include, but are not limited to, phospholipids, aminolipids, and sphingolipids. Representative phospholipids include sphingomyelin, phosphatidylethanolamine, phosphatidylcholine, phosphatidyserine, phosphatidylcholine, phosphatidylglycerol, palm itoyloylethanolamine, l-ceramide, ceramide, sphingosine, or sphingosine 1-phosphate. Suitable lipids include amphipathic lipids
medium. Alternatively, the liposomes of the pharmaceutical composition may be dried and micronized to one or more appropriate particle size either with or without added-exipients and administered by dry powder inhalation.

The average size of the one or more liposomes of the pharmaceutical composition may be less than about 10,000 nm, less than about 8,000 nm, less than about 5000 nm, less than about 4000 nm, less than about 3000 nm, less than about 2000 nm, less than about 1000 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm.

Time or Extended Release Formulations

In some instances, the pharmaceutical composition as provided herein may be formulated for timed release or slow-absorbing. The pharmaceutical composition may be formulated for timed release using one or more of a combination of liposomes. The physiochemical properties of liposomes such as size, bilayer fluidity, surface charge, as well as the method of preparation, affect their in vivo behavior. The vesicle size and number of bilayers are key parameters in determining the residence time of liposomes. Small liposomes (≤0.1 μm), for example, are optimized by macrophages less rapidly and to a lesser extent than large liposomes (>0.1 μm) and therefore may have a longer half-life. Small liposomes also release their contents at a slower rate. It should be appreciated that formulation of small liposomes for liquid aerosol or dry powder inhalation, for example, may include generating two or more particle sizes that are preferably in the range of 1-10 μm for optimal delivery to the pulmonary tissue and as such each particle may itself contain multiple smaller liposomes encapsulating the one or more agents of the pharmaceutical composition.

Bilayer fluidity may also influence the behavior of the liposomes. In general, lipids have a characteristic phase transition temperature, existing in different physical states above and below this temperature. The phase transition temperature may range from −20° C. to 90° C. and is dependent upon the length and saturation of the fatty acid side chains. Below the phase transition temperature, the lipids are in a rigid, well-ordered arrangement. Above the phase transition temperature, lipids are in a liquid-crystalline state or fluid phase. As such, liposomes composed of lipids with a phase transition temperature above physiological temperature, e.g., above 37° C., may be less fluid and hence less likely to leak their contents. As such, the fluidity of the liposome bilayer at various temperatures may be used to control release of liposome contents under physiological conditions.

Liposomes of the pharmaceutical composition may be further modified to modulate macropage-dependent clearance of the liposomes from the pulmonary tissue and as such modulate residence. In one aspect, the liposomes of the pharmaceutical composition as provided herein may include a polymer surface coating such as polyethylene glycol (PEG) which helps the liposome evade recognition and uptake by the immune system and thus prolong residence time of the pharmaceutical composition in the lung of the subject.

In a further aspect, the pharmaceutical composition may include formulations which release the one or more agent from the two or more particle sizes based on the microenvironment of the pulmonary tissue. In one aspect, the pharmaceutical composition may include one or more liposome formulations in which release of the encapsulated contents of the liposome is pH-sensitive. The pharmaceutical composition may include parenlyzer-caged liposomes in which preformed liposomes are treated with a cholesterol-functionalized poly(acrylic acid) additive, crosslinked, to become highly stable and have tunable pH-sensitive responses (see, e.g., Lee, et al., J. Am. Chem. Soc. 129:15096-15097, 2007, which is incorporated herein by reference). Additional examples of pH-sensitive liposomes are further described in Auguste, et al., J. Control Release [Epub ahead of print], 2008; U.S. Pat. Nos. 5,786,214, 5,965,434, 6,426,086, 6,897,196, 7,229,973, which are incorporated herein by reference.

Administration of a Pharmaceutical Composition

The pharmaceutical composition including at least one agent may be delivered by inhalation to a pulmonary tissue of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject may be delivered by inhalation using a nebulizer. The nebulizer may be a jet nebulizer in which compressed gas (air or oxygen) passes through a narrow orifice creating an area of low pressure at the outlet of an adjacent liquid feed tube. The pharmaceutical composition in solution is drawn up from the fluid reservoir and shattered into droplets in the gas stream. Alternatively, the nebulizer may be an ultrasonic nebulizer in which a piezoelectric crystal vibrates at a high frequency and generates a fountain of liquid in the nebulizer chamber. In this instance, the higher the frequency of vibration, the smaller the droplet size.

The pharmaceutical composition as provided herein may be delivered by inhalation using a metered liquid inhaler which produces a fine aerosol in the respirable range by forcing the pharmaceutical composition solution through an array of nozzles. The pattern of holes in the nozzle as well as the size and geometry of each hole may be modified to generate droplets of a desired size. These types of inhalers are exemplified by AerRx (Aradigm, Hayward, Calif., USA), AeroDose (AeroGen, Sunnyvale, Calif., USA), and Respimat (Boehringer Ingelheim, Ingelheim, Germany).

The pharmaceutical composition may be delivered by inhalation using a metered-dose inhaler in which the pharmaceutical composition aerosol is driven by propellants, e.g., hydrofluorocaranes. In some instances, the subject may manually actuate the inhaler followed by appropriate inhalation. Alternatively, the inhaler may be breath-actuated, firing in response to the subjects inspiratory effect.

Alternatively, the pharmaceutical composition may be delivered by inhalation using a dry powder inhaler. In this aspect, an aerosol of the pharmaceutical composition is created by directing air through loose powder. Dispersion of the powder into respirable particles depends on the creation of turbulent air flow within the powder container, causing aggregates to break up into particles small enough to be carried into the lower airways, if needed. The air flow may be generated by the subject. Alternatively, a battery driven propeller or compressed air may be used to aide in aerosolizing the powdered pharmaceutical composition.
In some instances, the pharmaceutical composition may be delivered directly to a subject using a personal nebulizer or inhaler as described herein. Alternatively, the pharmaceutical composition may be delivered to a subject or group of subjects in a room, building or other public space. For example, West describes a therapeutic air ventilator screen impregnated with a therapeutic agent for use in mediating the environment in a room (WIPO Patent WO/1999/030087, which is incorporated herein by reference). In some instances, the pharmaceutical composition including at least one agent to a pulmonary tissue of the subject, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject may be delivered to a subject or group of subjects as a fine mist released into a room or other space, e.g., an elevator, bus, train or airplane cabin. The fine mist containing the pharmaceutical composition may be delivered through a ventilation system. Alternatively, the fine mist containing the pharmaceutical composition may be delivered from one or more devices situated in the space with the flow of mist directed towards a given subject or group of subjects. The delivery device may be incorporated into other objects in the room such as a computer screen or keyboard or a telephone receiver or seat back. Alternatively, the pharmaceutical composition may be delivered to a subject or group of subjects in a specially designed and enclosed area. In one aspect, a fine mist may be released into a small tent such as an oxygen tent.

The methods and compositions are further described with reference to the following examples; however, it is to be understood that the methods, devices, and systems are not limited to such examples.

ILLUSTRATIVE EMBODIMENTS

Example 1

A method, system, or device is provided for receiving data including data of a physical condition affecting a subject or a group of subjects. The method, system, or device is further provided for sensing the physical condition affecting the subject or the group of subjects. Sensing the physical condition may include, but is not limited to, sensing environmental conditions such as smog, forest fires, volcanic ash, pollen count and weather conditions, such as temperature and humidity. The data regarding the physical condition may be acquired prior to the subject entering an environment where the physical condition exists. The method, system, or device provides data including data of the physical condition and sends the data from a sensing device to a receiving device on or in proximity to the subject or group of subjects, or to a third party, e.g., a physician or other caregiver, or to a combination thereof. Upon receiving information regarding the physical condition, a pharmaceutical composition may be administered in response to the physical condition wherein the pharmaceutical composition contacts the pulmonary tissue of the subject or group of subjects. The pharmaceutical composition includes at least one agent and may be configured to achieve a selected pH range in the pulmonary tissue of the one or more subjects, for the prevention and treatment of a viral infection, for example, prevention and treatment of influenza viral infection. The pharmaceutical composition may include one or more buffering agents to maintain a physiological pH in the subject or group of subjects. Alternatively, the pharmaceutical composition may include one or more of a basic agent, an acidic agent, or a buffering agent, or a combination thereof, to modify pulmonary pH in the one or more subjects. The pharmaceutical composition may be administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject for the prevention and treatment of a viral infection, for example, prevention and treatment of influenza viral infection. The pharmaceutical composition may further include one or more antiviral agent to treat viral pulmonary disease; one or more antihistamine or decongestant to treat the symptoms of viral or bacterial pulmonary disease or allergy; or a combination thereof.

A number of environment-related physical conditions may affect lung function or susceptibility to disease including, but not limited to, gases, particulates and other chemicals associated with smog, forest fires and volcanic disturbance as well as allergens, e.g., pollen and mold. Information regarding current and projected environmental conditions may be measured in a current location and or a future location and used to guide treatment of the pulmonary tissue with the pharmaceutical composition.

Data regarding an environmental condition may be received by one or more subjects from an agency or agencies that monitor and distribute data regarding various environmental conditions. Data regarding smog conditions in a given location may be received from one or more sources, e.g., the Environmental Protection Agency, NOAA-National Weather Service, NASA Earth Science, state and local air quality monitoring agencies. Data may be automatically received by a dedicated receiver device. Alternatively, the data may be received by a receiving device that is part of a cell phone, computer, personal digital assistant (PDA), pager, or other device for receiving information. Alternatively, data regarding an environmental condition may be sensed by a sensor associated with or in close proximity to one or more subjects. Data regarding the presence of unhealthy gases associated with smog, such as sulfur dioxide, nitrogen dioxide and carbon monoxide, may be measured using a hand held device carried by or in close proximity to one or more subjects.

Upon receiving or sensing data indicating an environmental condition, the device may alert one or more subjects and/or third party caregiver of the environmental condition. The device may provide data which recommends administration of the pharmaceutical composition to prevent or mitigate pulmonary infection. The one or more subjects and/or third party caregiver may choose to administer the pharmaceutical composition. Alternatively, a delivery device associated with the data receiving device may automatically administer the pharmaceutical composition to one or more subjects in response to an environmental condition. In one aspect, the pharmaceutical composition may be administered to a single individual using an inhaler. Alternatively, the pharmaceutical composition may be administered to a group of subjects as a fine mist, e.g., from a device or a ventilation system in a room or other confined space.

The pharmaceutical composition is formulated to deliver at least one agent to the pulmonary tissue. The pharmaceutical composition may contain one or more buffering agent to achieve a neutral pH of approximately 7.0 in the pulmonary tissue either in response to current exposure or in preparation for future exposure to a high concentration of...
sulfur dioxide due to poor air quality associated with forest fire smoke or volcanic disturbance.

Example 2

[0114] A method, system, or device is provided for receiving data including data of a physical condition affecting one or more subjects and for providing data by sensing the physical condition of the one or more subjects, and optionally including providing data by sensing the physiological condition of the one or more subjects. In one aspect, the data may inform administration of a pharmaceutical composition to the one or more subjects in response to the physical condition. The method, system, or device may sense the physical condition by communicating, providing, or receiving data on the physical condition utilizing one or more sensors located in the airway, e.g., nostril, sinus, trachea, of the subject. The one or more sensor may be further configured to monitor pH of the pulmonary tissue or pH of an exhalant of the subject. The one or more sensor may further be configured to monitor one or more parameters, including but not limited to, humidity of an exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, expiratory reserve volume, or residual volume of the one or more subjects. The one or more sensors automatically sends data to a second component of the device, e.g., a controller. Upon receiving information regarding the physical condition and/or the physiological condition of the one or more subjects, the second component, e.g., the controller, may send instructions to the device to administer a pharmaceutical composition to the pulmonary tissue of the subject, if needed. In one aspect, the pharmaceutical composition may include one or more buffering agents to maintain a physiological pH in the subject or group of subjects. Alternatively, the pharmaceutical composition may include one or more of a basic agent, an acidic agent, or a buffering agent, or a combination thereof, to modify pulmonary pH in the one or more subjects. The pharmaceutical composition may further include an antiviral agent to treat viral pulmonary disease, or an antiasthmatic or decongestant to treat viral or bacterial pulmonary disease or allergy. In a further aspect, the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject.

[0115] The method, system, or device includes one or more sensors that are configured to monitor a physiological condition of the subject, e.g., the pulmonary pH. The pulmonary pH of a subject may be measured in the exhaled breath condensate, which may consist of aerosolized particles of the airway lining fluid, water vapor condensation, and water soluble volatile gases. The one or more sensors are configured to monitor the pH of the exhaled breath condensate as an indicator of the pH of the pulmonary tissue. The one or more sensors for monitoring pH in the exhaled breath condensate may be sufficiently small to be located permanently or semi-permanently in one or more location of the airway of a subject. Alternatively, the one or more sensors may be incorporated into a dental or nasal prosthesis or into a piece of jewelry, for example, in a nose or tongue piercing. Alternatively, the one or more sensor for monitoring pH may be incorporated into a mask or other covering of the mouth and/or nose that is worn by the subject. The mask may be worn at all times, and as such continuously and in real time monitor exhaled breath condensate of a subject. Alternatively, the mask may be worn temporarily to monitor a subject’s exhaled breath condensate at any given point in time. In another aspect, the one or more sensor for monitoring pH may be a hand held device inserted into the oral cavity, the nasal cavity, or a combination thereof, of the subject.

[0116] The method, system, or device may further receive data regarding a physical condition of the subject that is an environmental condition. The environmental condition may be a condition posing an infectious risk. The infectious risk condition may be directly measured using one or more sensors to monitor air borne pathogens. Alternatively, the infectious risk condition may be inferred from a location, a time of the year, and previous pathogen outbreaks. In one aspect, data regarding the infection risk condition in a given location may be communicated, provided, or received by one or more agencies, e.g., a local or state Public Health agency, the Centers for Disease Control (CDC), the World Health Organization, or a combination thereof, and received by the device and communicated to the subject and/or a third party caregiver. The data of the infectious risk condition may be acquired prior to the subject entering an environment where the physical condition exists. The infectious risk condition of a subject in combination with the pulmonary tissue pH of a subject are communicated by the method, system, or device and may inform administration of the pharmaceutical composition.

[0117] Upon receipt by the device of data regarding the infection risk condition of a subject or by the device sensing data regarding the pulmonary tissue pH of a subject, or a combination thereof, a component of the device may analyze the incoming data and determine that administration of the pharmaceutical composition is appropriate under the current or predicted conditions. The device may receive and send instructions to automatically administer the pharmaceutical composition. Alternatively, the device may inform a subject and/or third party caregiver of the current or predicted conditions and the subject and/or third party caregiver may choose to administer the pharmaceutical composition.

[0118] In one aspect, the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of the pulmonary tissue and as such achieve two or more selected pH ranges in the two or more levels of the pulmonary tissue. In this aspect, different pH ranges may be achieved in different levels of the pulmonary tissue. This may facilitate directed treatment of that level of the pulmonary tissue that is infected by a virus while maintaining the microenvironment in other levels of the pulmonary tissue. For example, human influenza A and human rhinoviruses primarily infect epithelial cells in the upper airways of the pulmonary tissue. The first particle type of the composition may include one or more agents that is basic in pH or is a buffer that achieves a pH of greater than 7.0 and is sized by milling, formulation or liquid aerosolization to specifically deposit within regions of the upper airway, trachea and bronchus, e.g., with a diameter of about 3 to 6 μm. In a further aspect, the second particle type of the composition may achieve a pH ranging from 6.4 to 7.4 and is sized by milling, formulation, or liquid aerosolization to a smaller diameter that enables specific deposit within regions of the lower airway such as the bronchioles and alveoli, e.g., with a diameter of about 1 to 2 μm to maintain a normal pH level in a pulmonary tissue of the subject.

Example 3

[0119] A method, system, or device is described for receiving data of a physical condition affecting one or more subjects
and, optionally, for providing data by sensing the physiological condition of the one or more subjects. The data received by the device may include one or more of a location, a time, and a calendar entry of one or more subjects. The device may further receive or sense data of a physiological condition of one or more subjects, e.g., the pH within the pulmonary tissue. The data of the physical condition may be acquired prior to the subject entering an environment where the physiological condition exists. The method, system, or device communicates, provides, or receives data on the physical condition and sends the data from a sensing aspect to a receiving aspect of the device on or in proximity to the subject or group of subjects, or to a third party, e.g., a physician or other caregiver, or to a combination thereof. Upon receiving information regarding a current or future physical condition, a pharmaceutical composition may be administered to the lungs of the subject or group of subjects. The pharmaceutical composition includes at least one agent and may be configured to achieve a selected pH range of the pulmonary tissue of the one or more subjects. The pharmaceutical composition may include one or more buffering agents to maintain a physiological pH in the subject or group of subjects. Alternatively, the pharmaceutical composition may include one or more of a basic agent, an acid agent, or a buffering agent to modify pulmonary pH in the one or more subjects. The pharmaceutical composition may further include one or more antiviral agents to treat viral pulmonary disease, one or more antihistamines or decongestants to treat the symptoms of viral or bacterial pulmonary disease or allergy, or a combination thereof.

[0120] The method, system, or device may further include a global positioning device to monitor the current location of one or more subjects. The method or device further includes one or more calendar entries indicating scheduled activities, appointments, and/or outings of one or more subjects. The location and calendar entries may inform the device of one or more infectious risk conditions affecting the one or more subjects. In one aspect, the data regarding location and calendar entries may indicate when one or more subjects enter or intend to enter a location and are liable to be subject to increased risk of contracting a viral infection. A location with an increased risk of contracting a viral infection may be a crowded public space, a hospital, or a nursery, but not limited to, an airplane, a bus, a train, an office, a crowded city, a medical facility, a school, or a childcare facility. The method, system, or device may further receive data regarding current or anticipated pathogen outbreaks in a given location and at a given time of the year. As such, the location with an increased risk of contracting a viral infection may be a specific country and/or a specific location within that country.

[0121] The method, system, or device may further include one or more sensors for monitoring a physiological condition of one or more subjects. The method, system, or device may include sensors for monitoring the pulmonary pH of one or more subjects as provided herein. The infectious risk condition of one or more subjects is informed by data regarding the location and/or calendar entries of the one or more subjects in combination with data regarding the pulmonary tissue pH of the one or more subjects. These data are communicated by the method, system, or device and may inform administration of the pharmaceutical composition to the one or more subjects.

[0122] Upon receipt of data regarding the location and/or calendar entries of one or more subjects, or upon receipt of sensing data regarding the pulmonary tissue pH of a subject or group of subjects, or a combination thereof, a component of the device may analyze the incoming data and determine that administration of the pharmaceutical composition to the one or more subjects is appropriate under the current or predicted conditions. The device may provide instructions to automatically administer the pharmaceutical composition. Alternatively, the device may inform one or more subjects and/or third party caregivers of the current or predicted conditions and the one or more subjects and/or third party caregiver may choose to administer the pharmaceutical composition. In one aspect, a calendar entry and/or a location may indicate that a subject is about to board an airplane during a time of the year indicated as "flu season" by data received from a monitoring agency. In addition, one or more sensors may indicate that the subject’s current pulmonary pH is below the normal pH range. Upon receiving this data, a component of the device worn by the subject, e.g., a dental prosthesis, may receive instructions to administer the pharmaceutical composition to the one or more subjects. Alternatively, the subject may receive this data from the device and actively choose to administer the pharmaceutical composition using, e.g., a hand-held inhaler.

[0123] Each recited range includes all combinations and sub-combinations of ranges, as well as specific numerals contained therein.

[0124] All publications and patent applications cited in this specification are herein incorporated by reference to the extent not inconsistent with the description herein and for all purposes as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference for all purposes.

[0125] The herein described components (e.g., steps), devices, and objects and the description accompanying them are used as examples for the sake of conceptual clarity and that various configuration modifications using the disclosure provided herein are within the skill of those in the art. Consequently, as used herein, the specific exemplars set forth and the accompanying description are intended to be representative of their more general classes. In general, use of any specific exemplar herein is also intended to be representative of its class, and the non-inclusion of such specific components (e.g., steps), devices, and objects herein should not be taken as indicating that limitation is desired.

[0126] With respect to the use of substantially any plural or singular terms herein, those having skill in the art can translate from the plural to the singular or from the singular to the plural as is appropriate to the context or application. The various singular/plural permutations are not expressly set forth herein for sake of clarity.

[0127] The herein described subject matter sometimes illustrates different components contained within, or connected with, different other components. It is to be understood that such depicted architectures are merely exemplary, and that in fact many other architectures can be implemented which achieve the same functionality. In a conceptual sense, any arrangement of components to achieve the same functionality is effectively "associated" such that the desired functionality is achieved. Hence, any two components herein combined to achieve a particular functionality can be seen as "associated with" each other such that the desired functionality is achieved, irrespective of architectures or intermedial components. Likewise, any two components so associated can also be viewed as being "operably connected," or "operably coupled," to each other to achieve the desired function-
ality, and any two components capable of being so associated can also be viewed as being "operably coupleable", to each other to achieve the desired functionality. Specific examples of operably coupleable are not limited to physically mateable or physically interacting components or wirelessly interactable or wirelessly interacting components or logically interacting or logically interactable components.

While particular aspects of the present subject matter described herein have been shown and described, it will be apparent to those skilled in the art that, based upon the teachings herein, changes and modifications may be made without departing from the subject matter described herein and its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as are within the true spirit and scope of the subject matter described herein. Furthermore, it is to be understood that the invention is defined by the appended claims. It will be understood that, in general, terms used herein, and especially in the appended claims (e.g., body of the appended claims) are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least,") the term "includes" should be interpreted as "includes but is not limited to," etc.). It will be further understood that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to inventions containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an"; the same holds true for the use of definite articles such as an introduced claim recitations.

In addition, even if a specific number of an introduced claim recitation is explicitly recited, such recitation should typically be interpreted to mean at least the recited number (e.g., the bare recitation of "two recitations," without other modifiers, typically means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to "at least one of A, B, and C," etc., is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., "a system having at least one of A, B, and C") would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B, and C together, etc.). In those instances where a convention analogous to "at least one of A, B, or C," etc., is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., "a system having at least one of A, B, or C") would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, or A, B, and C together, etc.). Virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."
114. The device of claim 110, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject.

115. The device of claim 114, wherein the pharmaceutical composition includes a first agent in first-sized particles configured to maintain a first pH range in a first level of pulmonary tissue of the subject, and a second agent in second-sized particles configured to maintain a second pH range in a second level of pulmonary tissue of the subject.

116. The device of claim 97, wherein the pulmonary disease or condition is a viral pulmonary disease or a bacterial pulmonary disease.

117. The device of claim 97, wherein the one or more subjects are mammalian or avian.

118. A device comprising:
   a system including a signal-bearing medium including:
   instructions for providing data including data of a physical condition affecting one or more subjects, the data informing administration of a pharmaceutical composition in response to the physical condition, wherein the pharmaceutical composition contacts pulmonary tissue to treat a pulmonary disease or condition in the one or more subjects.

119. The device of claim 118, further comprising instructions for sensing the physical condition affecting the one or more subjects.

120. The device of claim 118, wherein the physical condition affecting the one or more subjects is an environmental condition, a signal from a global positioning device, a calendar entry, an environmental forecast, or a weather forecast.

121. The device of claim 120, further including instructions for providing data of a physiological condition of the one or more subjects.

122. The device of claim 120, wherein the calendar entry is configured to communicate data on the environmental condition, the environmental forecast, or the weather forecast.

123. The device of claim 121, wherein the calendar entry is configured to communicate data on the subject’s physiological condition.

124. The device of claim 118, wherein the data of the physical condition is acquired prior to the subject entering an environment where the physical condition exists.

125. The device of claim 120, wherein the global positioning device is configured to communicate data on a location of the one or more subjects.

126. The device of claim 119, wherein a sensor located on the subject detects the sensed physical condition.

127. The device of claim 126, wherein the sensor is located in a sinus or nostril of the subject.

128. The device of claim 126, wherein the sensor is configured to monitor pH of the pulmonary tissue or pH of an exhalant in the subject.

129. The device of claim 126, wherein the sensor is configured to monitor humidity of an exhalant, temperature, breathing rate, peak rate of exhalation, tidal volume, vital capacity, inspiratory capacity, expiratory reserve volume, or residual volume.

130. The device of claim 118, wherein a third party advises or controls the administration of the pharmaceutical composition to the one or more subjects.

131. The device of claim 118, wherein the pharmaceutical composition includes at least one agent and is configured to achieve a selected pH range of the pulmonary tissue of the one or more subjects.

132. The device of claim 131, wherein the at least one agent includes at least one buffering agent.

133. The device of claim 131, wherein the at least one agent includes at least one basic agent.

134. The device of claim 131, wherein the at least one agent includes at least one acidic agent.

135. The device of claim 131, wherein the pharmaceutical composition is administered as two or more distinct and non-overlapping particle size ranges configured to contact two or more levels of pulmonary tissue of the subject, wherein the at least one agent is configured to achieve a selected pH range in the two or more levels of pulmonary tissue of the subject.

136. The device of claim 135, wherein the pharmaceutical composition includes a first agent in first-sized particles configured to maintain a first pH range in a first level of pulmonary tissue of the subject, and a second agent in second-sized particles configured to maintain a second pH range in a second level of pulmonary tissue of the subject.

137. The device of claim 118, wherein the pulmonary disease or condition is a viral pulmonary disease or bacterial pulmonary disease.

138. The device of claim 118, wherein the one or more subjects are mammalian or avian.

* * * * *