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DESCRIPTION

Field

[0001] The subject technology relates generally to apparatuses and methods for delivery of substances, e.g., delivery of medication to the lungs using by inhalation for treating disease.

Summary

[0002] An aspect of at least one embodiment disclosed herein includes the recognition of a need for improved apparatuses and methods for delivery of drugs for treating disease that utilize a dosage that is effective to reduce a risk of a thromboembolic event in a patient, lower than traditional dosages, and administered using a more direct delivery mechanism to the systemic blood stream. The invention is defined by the appended claims.

Thromboembolic Symptoms and Events

[0003] A thromboembolic event, such as myocardial infarction, deep venous thrombosis, pulmonary embolism, thrombotic stroke, etc., can present with certain symptoms that allow a patient or clinician to provide an initial therapy or treatment for the event. In some situations, an 81 mg, low dose, or baby aspirin or a regular aspirin (330 mg) may be orally administered in order to provide an initial treatment for the patient.

[0004] According to some embodiments disclosed herein is the realization that this treatment may not act as quickly as necessary to provide a sufficient therapeutic effect and therefore, may lead to a less preferred outcome. Thus, in some embodiments, a drug delivery system and related methods are disclosed that provide an accelerated and more efficient pathway and treatment for reducing the risk of a thromboembolic event and/or providing treatment for a thromboembolic event. For example, some embodiments provide systems and methods of administering a nonsteroidal anti-inflammatory drug ("NSAID") by inhalation, such as by a dry powder inhaler ("DPI") or a metered dose inhaler ("MDI").

Delivery Mechanisms for Drugs

[0005] Drugs can be administered orally in different ways, such as liquids, capsules, tablets, or chewable tablets. The oral route is used most often because it is the most convenient, safest, and least expensive. However, oral drug delivery has limitations because of the way a drug typically moves through the digestive tract.

[0006] For example, when a drug is administered orally, it is absorbed in the mouth, stomach, and the small intestine. Before the drug enters the bloodstream, it must pass through the intestinal wall and travels to the liver. While passing through the intestinal wall and liver, the drug is metabolized, which can decrease the amount of the drug that actually reaches the bloodstream. The metabolism of the drug reduces the bioavailability of the drug and is often termed the "first pass effect." The fraction of the drug lost during due to the first pass effect is generally determined by absorption in the liver and gut wall, and gastrointestinal lumen enzymes, gut wall enzymes, bacterial enzymes, and hepatic (liver) enzymes.

[0007] Generally, the first pass effect on aspirin significantly reduces the bioavailability of the administered dosage. For example, due to the acidic conditions in the stomach, aspirin is absorbed in the stomach and the upper small intestine. After being absorbed, aspirin is metabolized to acetic acid and salicylate. When taken orally, generally only about one to two-thirds of the dose of aspirin is bioavailable due to the first pass effect.

[0008] For example, in Iwamoto K., GASTROINTESTINAL AND HEPATIC FIRST-PASS METABOLISM OF ASPIRIN IN RATS, J Pharm Pharmacol. 1982 Mar; 34(3), pp. 176-80, the study examines the absorption of aspirin in four male subjects following an oral solution of 650 mg. As stated in the study report, "the absorption process appeared to follow first-order kinetics, with a half-life ranging from 4.5 to 16.0 min. between subjects. Comparison of the area under the aspirin plasma concentration-time curve following intravenous and oral routes indicated that only 68% of the dose reached the peripheral circulation intact."

[0009] Applicant has determined that even drugs that are administered by inhalation undergo a first pass effect. For drug administration by inhalation, smaller particles proceed via a nasal route, down the windpipe (trachea) and into the lungs. The size of the particles can be determinative of the overall efficacy of the treatment. Once inside the lungs, these particles are absorbed into the bloodstream.

[0010] Few drugs are administered by inhalation because the dosage of an inhaled drug, as well as the delivery timing, can often be difficult to measure. Usually, this method is used to administer drugs that act specifically on the lungs, such as aerosolized antiasthmatic drugs in metered-dose containers, and to administer gases used for general anesthesia.

Pharmacokinetics of Aspirin

[0011] Aspirin is the acetylated form of salicylic acid, and the active chemical in aspirin is called acetylsalicylic acid (ASA). Aspirin is used by millions of people to achieve desirable effects, and by many people, baby aspirin is often used daily. The principal effect of aspirin is to impair the function of cyclooxygenase enzymes (specifically, COX1 and COX2 enzymes).

[0012] By inhibiting COX1, aspirin can irreversibly inhibit platelet aggregation, which decreases

the risk of blood clots. Additionally, the impairment of the COX2 enzyme can reduce inflammation, stiffness, and pain in the body by inhibiting prostaglandins and thromboxanes. As such, individuals at high risk for heart attack, stroke, or with inflammation often take aspirin to address symptoms and effects of these conditions. As noted, aspirin can effectively reduce the likelihood of such myocardial events and reduce pain and inflammation with a dose as small as a baby aspirin. However, due at least in part to its inhibition of COX1, aspirin can increase the risk of bleeding and cause damage to organs such as the stomach and intestines, which can be painful.

Dry Powder Inhaler Technology

[0013] As stated above, the oral delivery of aspirin may create a risk of damage to the stomach wall leading to pain, indigestion and a high risk of bleeding. Further, according to at least one of the aspects of embodiments disclosed herein is the realization that it is often difficult to orally administer a drug during emergency situations that may implicate or result in a thromboembolic event. For example, the patient may be experiencing vomiting or otherwise be unable to take the drug orally. Additionally, oral administration of a drug may be undesirable because the drug does not reach the systemic blood stream immediately, thus delaying the important effects of the drug. Even so, due to the first pass effect in the liver and gut, the amount of drug reaching systemic circulation is much less than that administered. Therefore, according to aspects of various embodiments disclosed herein is the realization that an alternative route of administration could avoid these unwanted side-effects.

[0014] Various embodiments disclosed herein reflect the novel realization that delivery of a drug by inhalation in the early stages of an emergency situation can provide a fast-acting, effective form of preliminary treatment of certain medical conditions. For example, in some embodiments, upon receiving a complaint of a symptom of a serious thromboembolic event, a patient can be administered, by DPI, a therapeutic amount of a NSAID. The NSAID can address problems associated with or provide an initial treatment for the medical condition.

[0015] However, dry powder inhalation of drugs has generally been limited by cough, to dosages of less than a milligram. Recent developments in particle engineering, in particular the development of PulmoSphere™ technology, have enabled the delivery of a larger amount of dry powder to delivered to the lungs in a single actuation. *See* David E. Geller, M. D., et al., DEVELOPMENT OF AN INHALED DRY-POWDER FORMULATION OF TOBRAMYCIN USING PULMOSPHERE™ TECHNOLOGY, J Aerosol Med Pulm Drug Deliv. 2011 August; 24(4), pp. 175-82. In this publication, a dose of 112 mg tobramycin (in four capsules) was effectively delivered via PulmoSpheres™.

[0016] In accordance with some embodiments is the realization that the body includes various particle filters that limit the efficacy of inhaled drugs. For example, the oropharynx tends to prevent passage of particles having a diameter greater than 5 μm. However, in order to reach

the alveoli, particles must have a size from about 1 µm to about 5 µm. Accordingly, one can prepare and use inhalable aspirin using technology similar to PulmoSpheres™ as disclosed herein to produce particles with a median geometric diameter of from about 1 µm to about 5 µm, and in some embodiments, from about 1.7 µm to about 2.7 µm.

[0017] There has been no single dose use of aspirin by dry powder inhaler to replace the traditional daily use of a NSAID (such as a baby aspirin) or emergency use of a NSAID as preventative care for symptoms of a thromboembolic event. Accordingly, provided herein is the administration of a NSAID by dry powder inhalation in an amount less than the dosage of a baby aspirin (i.e., less than 81 mg).

[0018] The invention is aimed at reducing the risk of a thromboembolic event using the NSAID acetylsalicylic acid, as set out in the appended set of claims. To do so, one can administer acetylsalicylic acid by a DPI. The administered dosage can be less than 25 mg of acetylsalicylic acid. Further, the administered dosage can be less than 20 mg of acetylsalicylic acid. The administered dosage can be less than 15 mg of acetylsalicylic acid. The administered dosage can also be less than 12 mg of acetylsalicylic acid. The administered dosage can be less than 10 mg of acetylsalicylic acid. Furthermore, the administered dosage can be less than 8 mg of acetylsalicylic acid. The administered dosage can be less than 5 mg of acetylsalicylic acid. In some embodiments, the administered dosage can be less than 2 mg of acetylsalicylic acid.

[0019] For example, according to some embodiments, the dosage can be from about 2 mg to about 30 mg of acetylsalicylic acid. In some embodiments, the dosage can be from about 4 mg to about 25 mg of acetylsalicylic acid. The dosage can be from about 6 mg to about 20 mg of acetylsalicylic acid. Further, in some embodiments, the dosage can be from about 8 mg to about 15 mg of acetylsalicylic acid. Further, in some embodiments, the dosage can be from about 10 mg to about 13 mg of acetylsalicylic acid. For example, in some embodiments, the dosage can be about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, or 20 mg of acetylsalicylic acid.

[0020] Additionally, the dose of acetylsalicylic acid can be less than about 80 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 1 mg to about 75 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 2 mg to about 60 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 5 mg to about 40 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 10 mg to about 30 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 12 mg to about 25 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 15 mg to about 20 mg.

[0021] In accordance with some embodiments, such dosages can provide a bioequivalent dosage when compared to typical dosages of 81 mg to about 325 mg, while demonstrating few negative side effects.

[0022] Thus, aspirin can be administered by DPI in a single dose that is much less than a

traditional oral dose of aspirin, which can provide a bioequivalent equivalent treatment while tending to avoid the negative side effects associated with aspirin.

[0023] The DPI can have a mouthpiece and an actuation member for making available the NSAID for inhalation by a patient to reduce the risk of the thromboembolic event.

[0024] For example, according to some embodiments, in order to reduce the risk of a thromboembolic event one can administer the dose of the nonsteroidal anti-inflammatory drug by a dry powder inhaler. The dose can be effective to reduce a risk of a thromboembolic event in a patient. The dry powder inhaler can have a mouthpiece and an actuation member for making available the dose of the nonsteroidal anti-inflammatory drug for inhalation by the patient to reduce the risk of the thromboembolic event.

[0025] A drug delivery system can also be used according to some embodiments, for reducing the risk of a thromboembolic event. The system can comprise the dose of the nonsteroidal anti-inflammatory drug in powder form. The dose can be effective to reduce a risk of a thromboembolic event in a patient. The system can also comprise a dry powder inhaler. The dry powder inhaler can have a mouthpiece, a reservoir for receiving the dose of the nonsteroidal anti-inflammatory drug, and an actuation member for making available the dose of the nonsteroidal anti-inflammatory drug for inhalation by the patient through the mouthpiece.

[0026] In some embodiments, the thromboembolic event comprises at least one of myocardial infarction, deep venous thrombosis, pulmonary embolism, or thrombotic stroke. The dose of the nonsteroidal anti-inflammatory drug can be administered as a preliminary treatment in response to a symptom of a thromboembolic event. The nonsteroidal anti-inflammatory drug is aspirin. Further, the dose of the nonsteroidal anti-inflammatory drug is administered in a single dose.

Brief Description of the Drawings

[0027] The accompanying drawings, which are included to provide further understanding of the subject technology and are incorporated in and constitute a part of this specification, illustrate aspects of the subject technology and together with the description serve to explain the principles of the subject technology.

Figure 1 is a schematic view of a patient using a dry powder inhaler, in accordance with some implementations of the methods and systems disclosed herein.

Figure 2A-F illustrate usages and a configuration of a dry powder inhaler, according to some embodiments.

Detailed Description

[0028] In the following detailed description, numerous specific details are set forth to provide a full understanding of the subject technology. It will be apparent, however, to one ordinarily skilled in the art that the subject technology may be practiced without some of these specific details. In other instances, well-known structures and techniques have not been shown in detail so as not to obscure the subject technology.

[0029] A phrase such as "an aspect" does not imply that such aspect is essential to the subject technology or that such aspect applies to all configurations of the subject technology. A disclosure relating to an aspect may apply to all configurations, or one or more configurations. An aspect may provide one or more examples of the disclosure. A phrase such as "an aspect" may refer to one or more aspects and vice versa. A phrase such as "an embodiment" does not imply that such embodiment is essential to the subject technology or that such embodiment applies to all configurations of the subject technology. A disclosure relating to an embodiment may apply to all embodiments, or one or more embodiments. An embodiment may provide one or more examples of the disclosure. A phrase such "an embodiment" may refer to one or more embodiments and vice versa. A phrase such as "a configuration" does not imply that such configuration is essential to the subject technology or that such configuration applies to all configurations of the subject technology. A disclosure relating to a configuration may apply to all configurations, or one or more configurations. A configuration may provide one or more examples of the disclosure. A phrase such as "a configuration" may refer to one or more configurations and vice versa.

[0030] As discussed above, although NSAIDs, such as aspirin, can provide various beneficial effects and contribute to reducing the likelihood of a thromboembolic event, there may be some drawbacks to their use. Further, the use of NSAIDs, such as aspirin, in a clinical setting has traditionally been limited to oral administration. Oral administration of aspirin, for example, can result in the loss or inactivation of approximately 2/3 of the oral dosage due to the first pass effect in the gut and liver. While one third of the dosage reaches the systemic blood stream and provides the desired effect, the negative side effects created by the full dosage often deter patients from using aspirin on a regular or daily basis.

[0031] Further, in many situations, such as in emergencies, oral administration of NSAIDs, such as aspirin, may be inappropriate because it may take too long to be effective. According to at least one aspect of some embodiments disclosed herein is the realization that an alternative administration method and systems can be implemented that utilize a lower dosage and provide a more direct delivery mechanism to the systemic blood stream. Thus, some embodiments disclosed herein allow for the beneficial effects of NSAIDs, such as aspirin, to be achieved on a regular basis and in emergency situations, while minimizing previous drawbacks associated with the use of NSAIDs.

[0032] Various studies have determined that aspirin has a significant effect on reducing the risk of myocardial infarction. However, these studies presented inconclusive data on strokes,

pulmonary embolism, or deep venous thrombosis. These studies have used aspirin dosages of 325 mg, However, these studies have based their findings on oral administration of aspirin and have not suggested DPI or MDI pathways, which are provided in some embodiments disclosed herein. Further, the administration of aspirin has negative side effects, such as significantly increasing major gastrointestinal and extracranial bleeds by over 50%. This has led some to argue that for preventative treatment, aspirin is of uncertain net value.

[0033] Further studies have tested whether the benefits of aspirin could be obtained at low dosages, such as that of baby aspirin (i.e., 81 mg). The Swedish Aspirin Low-dose Trial (SALT) found that a low dose (75 mg/day) of aspirin significantly reduces the risk of stroke or death in patients with cerebrovascular ischaemic events. However, the study also reported gastrointestinal side-effects that included a significant excess of bleeding episodes. A Danish study found that patients receiving aspirin as an antithrombotic agent achieved satisfactory platelet inhibition with 50 mg/day, while the remainder of the patients needed over 50 mg/day. Furthermore, a Dutch TIA Study concluded that aspirin at any dose above 30 mg daily prevents 13% of vascular events, and that there is a need for more efficacious drugs. However, no study or teaching has been provided regarding the administration of aspirin by DPI or MDI at very low doses.

[0034] Additionally, Applicants note that although inhaled dry powder formulations of aspirin have been developed, reports have stated that the formulation was not clinically feasible because it is difficult to meet the high dosage requirements of aspirin (-80 mg/day for low-dose prevention of coronary events and stroke, and at least 300 mg/day for pain or fever relief) via pulmonary delivery of dry powders.

[0035] In addition, these reports recognize that adverse effects of dry powder on the lungs, such as coughing, cannot be avoided unless the doses are less than a few tenths of a milligram in a single breath. Thus, prior teachings suggest that higher dosage requirements of aspirin would be impossible to meet using DPI. Finally, some have taught that there is a higher incidence of aspirin intolerance in asthmatic patients when aspirin is delivered by inhalation than orally.

[0036] In yet another study, the authors noted that use of nanoparticulate drugs for dry powder inhaler (DPI) delivery is not straightforward. Direct inhalation of nanoparticulate drugs was infeasible due to their small size. The nanometer size leads to the nanoparticulate drugs being predominantly exhaled from the lungs, without any deposition taking place. Moreover, a severe aggregation problem arising from the small size makes their physical handling difficult for DPI delivery. Accordingly, "large hollow carrier particles" of nanoparticulate drugs has been developed for pulmonary delivery of some drugs. See Hadinoto et al., Drug Release Study Of Large Hollow Nanoparticulate Aggregates Carrier Particles For Pulmonary Delivery, International Journal of Pharmaceutics 341 (2007) 195-20.

[0037] In the Hadinoto study, the authors used aspirin as a model for "lowly watersoluble" drugs. The authors acknowledged that "with regard to the aspirin, the nanoparticulate polymer

delivery method is not the most suitable method of delivery due to the high dosage requirement of aspirin (-300 mg/day)," and overall, the aim of the study was to identify key facets in the formulation of the large hollow nanoparticulate aggregates. *See id.* US2002/158150 also discloses particles of aspirin for pulmonary delivery by means of a dry powder inhaler.

[0038] The invention as disclosed herein is aimed at reducing the risk of a thromboembolic event by administration of a very a low dose of aspirin, by DPI. The dose is much less than that of a baby aspirin (less than 81 mg). The administered dosage can be less than 25 mg of acetylsalicylic acid. Further, the administered dosage can be less than 20 mg of acetylsalicylic acid. The administered dosage can be less than 15 mg of acetylsalicylic acid. The administered dosage can also be less than 12 mg of acetylsalicylic acid. The administered dosage can be less than 10 mg of acetylsalicylic acid. Furthermore, the administered dosage can be less than 8 mg of acetylsalicylic acid. The administered dosage can be less than 5 mg of acetylsalicylic acid. In some embodiments, the administered dosage can be less than 2 mg of acetylsalicylic acid.

[0039] For example, according to some embodiments, the dosage can be from about 2 mg to about 30 mg. In some embodiments, the dosage can be from about 4 mg to about 25 mg of acetylsalicylic acid. The dosage can be from about 6 mg to about 20 mg of acetylsalicylic acid. Further, in some embodiments, the dosage can be from about 8 mg to about 15 mg of acetylsalicylic acid. Further, in some embodiments, the dosage can be from about 10 mg to about 13 mg of acetylsalicylic acid. For example, in some embodiments, the dosage can be about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, or 20 mg of acetylsalicylic acid.

[0040] Additionally, the dose of acetylsalicylic acid can be less than about 80 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 1 mg to about 75 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 2 mg to about 60 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 5 mg to about 40 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 10 mg to about 30 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 12 mg to about 25 mg. In some embodiments, the dose of acetylsalicylic acid can be from about 15 mg to about 20 mg.

[0041] Such dosages can provide a bioequivalent dosage when compared to typical dosages of 81 mg to about 325 mg, while demonstrating few negative side effects.

[0042] Referring to Figure 1, in a dry powder inhalation technique, a patient can use a dry powder inhaler 10 to inhale a powder formulation of a drug, such as a NSAID. The dose is effective to reduce a risk of a thromboembolic event in the patient. An aspect of some embodiments is the realization that because the lung is an efficient filter, it generally only permits particles having a size of less than 5 μm. For example, after the drug enters the main stem bronchus 20, the drug will enter each lung 22, 24. The drug can then pass through the

bronchial trees 26, 28 until reaching the individual alveoli 30 in the lungs 22, 24, which are exceedingly numerous, as discussed below. Thus, the dry powder inhaler 10 can allow the patient to self administer a dosage of particles having a size of from about 1 µm and about 5 µm. In some embodiments, the particle size can be from about 2 µm to about 4 µm.

[0043] According to some embodiments, various types of inhalers can be used to provide the drug using a DPI delivery system. The dose administered can be effective to reduce a risk of a thromboembolic event in a patient.

[0044] For example, the dry powder inhaler 10 can comprise a mouthpiece, a reservoir for receiving the NSAID, and an actuation member for making available the NSAID for inhalation by a patient through the mouthpiece.

[0045] For example, Figures 2A-2F illustrate a DPI delivery device 100 having a mouthpiece 102 and a drug compartment 104. The drug compartment 104 can be inserted into an inhaler body cavity 110.

[0046] For example, as shown in Figure 2B, the drug compartment 104 can be inserted into the body cavity 110 into a stowed position 120 for storage purposes. However, the drug compartment 104 can also be moved to a first position 122, shown in Figure 2C, in which a first receptacle 140 of the drug compartment 104 is aligned with a mouthpiece airway 142. In this first position 122, the drug contained in the first receptacle 140 can be delivered through the mouthpiece airway 142 to be inhaled by the patient, as illustrated in Figure 2D.

[0047] Additionally, as shown in Figure 2E, the drug compartment 104 can be moved to a second position 124 in which a second receptacle 144 is aligned with the mouthpiece airway 142. Thus position, the drug contained in the second receptacle 144 can be inhaled by the patient, as illustrated in Figure 2F.

[0048] NSAIDs can include salicylates, i.e., the salts and esters of salicylic acid, that have anti-platelet action, as well as one or more of the following:

Aspirin (Aspirin is a brand name; the chemical is called acetylsalicylic acid)
Celecoxib (Celebrex)
Dexdetoprofen (Keral)
Diclofenac (Voltaren, Cataflam, Voltaren-XR)
Diflunisal (Dolobid)
Etodolac (Lodine, Lodine XL)
Etoricoxib (Algix)
Fenoprofen (Fenopron, Nalfron)
Firocoxib (Equioxx, Previcox)
Flurbiprofen (Urbifen, Ansaid, Flurwood, Froben)

Ibuprofen (Advil, Brufen, Motrin, Nurofen, Medipren, Nuprin)
Indomethacin (Indocin, Indocin SR, Indocin IV)
Ketoprofen (Actron, Orudis, Oruvail, Ketoflam)
Ketorolac (Toradol, Sprix, Toradol IV/IM, Toradol IM)
Licofelone (under development)
Lornoxicam (Xefo)
Loxoprofen (Loxonin, Loxomac, Oxeno)
Lumiracoxib (Prexige)
Meclofenamic acid (Meclomen)
Mefenamic acid (Ponstel)
Meloxicam (Movalis, Melox, Recoxa, Mobic)
Nabumetone (Relafen)
Naproxen (Aleve, Anaprox, Midol Extended Relief, Naprosyn, Naprelan)
Nimesulide (Sulide, Nimalox, Mesulid)
Oxaporozin (Daypro, Dayrun, Duraprox)
Parecoxib (Dynastat)
Piroxicam (Feldene)
Rofecoxib (Vioxx, Ceoxx, Ceeoxx)
Salsalate (Mono-Gesic, Salflex, Disalcid, Salsitab)
Sulindac (Clinoril)
Tenoxicam (Mobiflex)
Tolfenamic acid (Clotam Rapid, Tufnil)
Valdecoxib (Bextra)

[0049] Other alternatives can also be used instead of a NSAID, which include Plavix (clopidogrel), COX-2 inhibitors, other remedies such as Nattokinase (an enzyme (EC 3.4.21.62, extracted and purified from a Japanese food called natto). The present invention relies on aspirin. It is contemplated that the effects, pharmacokinetic data, and other considerations relating to aspirin can be equally applied to other NSAIDs.

[0050] Through some of the embodiments disclosed herein, the inventors have overcome the challenges acknowledged by prior teachings. In particular, the inventors have recognized that when a drug is inhaled into the lungs, the drug can be dispersed toward the alveoli. Although alveoli primarily function to exchange carbon dioxide for oxygen, alveoli also produce enzymes. Thus, inhaled substances, such as pathogens, drugs, or other chemicals, may be processed at the alveoli.

[0051] An alveolus comprises a network of elastic fibers and capillaries, resembling a woven

sphere on its outer surface. The capillaries function to carry oxygen depleted blood toward the lungs and oxygen rich blood away from the lungs, via the pulmonary artery and the pulmonary vein. The interior of each alveoli comprises a thin tissue known as an alveolar lining or epithelium. Alveolar epithelium is made of two distinct types of cells, known as flat type I and type II. Flat type I cells cover most of the surface area of the epithelium and are closely spaced, allowing only small molecules to pass therebetween, such as oxygen and carbon dioxide. Type II alveolar cells aid in producing the pulmonary surfactant used in gas exchange. Further, the alveolar epithelium also comprises macrophages, which assist in disposing of fine particulate foreign matter such as dust, tar, and pathogens. Despite the diminutive size of the alveoli (being only approximately 250 μm), because an adult can have between 200 million and 400 million alveoli, the alveolar respiratory surface area can be from approximately 1,400 to about 1,600 square feet.

[0052] As disclosed herein, absorption of NSAIDs administered by DPI or MDI through the pulmonary capillaries and epithelium can provide an immediately effective treatment to address symptoms of thromboembolic events. One of the novel realizations of some embodiments is that the substantial first pass effect produced by oral administration of NSAIDs, herein aspirin, can be avoided through administration by dry powder inhaler. In addition, there has hitherto been no teaching or suggestion regarding the pharmacokinetics of dry powder delivery of a NSAID, herein aspirin, and the possible metabolism or inactivation of the drug as it encounters the endothelial tissue of the pulmonary capillaries.

[0053] The delivery of a NSAID by DPI or MDI is a complex and unpredictable technological area that has not provided straightforward or expected results to a person of skill in the art. Accordingly, there has been no reason for a person of skill to believe that a combination of prior systems or treatment methods could produce the embodiments disclosed herein. For example, some embodiments herein recognize an unexpected result that as a drug crosses the endothelium of pulmonary arteries and alveoli, the first pass effect is minimized and results in a much lower rate of the activation of the drug than in other drug delivery pathways.

[0054] The endothelium of the pulmonary capillaries serve as a barrier by selectively allowing materials to exit or enter the bloodstream. It would be expected that aspirin would be inactivated in the pulmonary capillaries, which are lined by endothelial cells. The endothelial cells are extremely metabolically active. Thus, a person of skill would expect that aspirin would be inactivated by the endothelium of the pulmonary capillaries. However, according to some embodiments disclosed herein, it is contemplated that as the powdered drug encounters the endothelium, the endothelium can metabolize or activate a much smaller portion of the powdered drug compared to the metabolism provided by the gut and liver. For example, after being transformed in the stomach to salicylic acid, as much as 80% of the salicylic acid is metabolized in the liver. Thus, only a small minority of the salicylic acid is bioavailable to the systemic blood stream.

[0055] However, it is contemplated that a vast majority of the salicylic acid metabolized from the inhaled aspirin powder will be bioavailable to the systemic blood stream. Thus, a dose of

much less than that of a baby aspirin (less than 81 mg) is provided by dry powder inhalation. This can provide a much lower dosage while providing a bioequivalent dosage.

[0056] Further, in accordance with an aspect of some embodiments, it is contemplated that an analogous first pass effect may be experienced in the endothelium of the pulmonary capillaries. Accordingly, with regard to the provision of an inhaled dosage that is the bioequivalent of a baby aspirin administered orally, the inhaled dosage should account for some first pass effect experience through the endothelium of the pulmonary capillaries.

[0057] In accordance with some embodiments, the first pass effect through the endothelium of the pulmonary capillaries can be a minimum, which provides little overall effect on the inhaled dosage.

[0058] However, it is also contemplated that in some embodiments, the first pass effect through the endothelium of the pulmonary capillaries can be entirely negligible. Thus, the amount of the inhaled dosage need not be adjusted to compensate for first pass effect through the pulmonary capillaries.

[0059] Therefore, some embodiments recognize the unexpected result that even extremely low doses of aspirin (and likely other NSAIDs) can provide a significant therapeutic effect while providing to minimus or inconsequential side effects. For example, doses as low as 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg of acetylsalicylic acid can be effective in reducing the risk of a thromboembolic event. Accordingly, the net benefits increased dramatically at significantly lower doses, according to some embodiments. These results and outcomes are unexpected given the complex and unpredictable nature of drug interactions in the body, drug delivery pathways, and microscopic drug structures. Finally, no teachings or other prior references disclose a system or process for achieving therapeutically beneficial results while substantially avoiding any negative side effects using DPI or MDI drug delivery mechanisms with microscopic NSAIDs.

[0060] In accordance with some embodiments, the dry powder administration of the NSAID acetylsalicylic acid, can comprise particles having a size of from about 1 μm to about 5 μm, as discussed above. The particles can be highly porous and demonstrate a sponge-like morphology or be a component of a carrier particle. The particles can also demonstrate a spheroidal shape, by which the shape and porous surface can serve to decrease the area of contact between particles, thereby leading to less particle agglomeration and more effective distribution throughout the lung. Dry powder technologies, such as PulmoSphere™, may be implemented in embodiments of the methods and systems disclosed herein.

[0061] As used herein, the phrase "at least one of" preceding a series of items, with the term "and" or "or" to separate any of the items, modifies the list as a whole, rather than each member of the list (i.e., each item). The phrase "at least one of" does not require selection of at least one of each item listed; rather, the phrase allows a meaning that includes at least one of any one of the items, and/or at least one of any combination of the items, and/or at least one

of each of the items. By way of example, the phrases "at least one of A, B, and C" or "at least one of A, B, or C" each refer to only A, only B, or only C; any combination of A, B, and C; and/or at least one of each of A, B, and C.

[0062] Terms such as "top," "bottom," "front," "rear" and the like as used in this disclosure should be understood as referring to an arbitrary frame of reference, rather than to the ordinary gravitational frame of reference. Thus, a top surface, a bottom surface, a front surface, and a rear surface may extend upwardly, downwardly, diagonally, or horizontally in a gravitational frame of reference.

[0063] Furthermore, to the extent that the term "include," "have," or the like is used in the description or the claims, such term is intended to be inclusive in a manner similar to the term "comprise" as "comprise" is interpreted when employed as a transitional word in a claim.

[0064] The word "exemplary" is used herein to mean "serving as an example, instance, or illustration." Any embodiment described herein as "exemplary" is not necessarily to be construed as preferred or advantageous over other embodiments.

[0065] A reference to an element in the singular is not intended to mean "one and only one" unless specifically stated, but rather "one or more." Pronouns in the masculine (e.g., his) include the feminine and neuter gender (e.g., her and its) and vice versa. The term "some" refers to one or more. Underlined and/or italicized headings and subheadings are used for convenience only, do not limit the subject technology, and are not referred to in connection with the interpretation of the description of the subject technology. Moreover, nothing disclosed herein is intended to be dedicated to the public regardless of whether such disclosure is explicitly recited in the above description.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US2002158150A [0037]

Non-patent literature cited in the description

- **IWAMOTO K.**GASTROINTESTINAL AND HEPATIC FIRST-PASS METABOLISM OF ASPIRIN IN RATSJ Pharm Pharmacol, 1982, vol. 34, 3176-80 [0008]
- **DAVID E. GELLERM. D. et al.**DEVELOPMENT OF AN INHALED DRY-POWDER FORMULATION OF TOBRAMYCIN USING PULMOSPHERE™ TECHNOLOGYJ Aerosol Med Pulm Drug Deliv, 2011, vol. 24, 4175-82 [0015]
- **HADINOTO et al.**Drug Release Study Of Large Hollow Nanoparticulate Aggregates Carrier Particles For Pulmonary DeliveryInternational Journal of Pharmaceutics, 2007, vol. 341, 195-20 [0036]

Patentkrav

1. Acetylsalicylsyre til anvendelse til at reducere risikoen for en tromboembolisk hændelse hos et individ med behov derfor, hvor en enkelt dosis på mindre end 81 mg, fortrinsvis mindre end 80 mg, af acetylsalicylsyre administreres ved inhalation af tørt pulver til nævnte individ.

2. Acetylsalicylsyre til anvendelse ifølge krav 1, hvor dosen af acetylsalicylsyre administreres af en tørpulverinhalator, hvor tørpulverinhalatoren har et mundstykke og et aktiveringselement til at stille dosen af acetylsalicylsyren til rådighed til inhalation af patienten for at reducere risikoen for den tromboemboliske hændelse.

3. Acetylsalicylsyre til anvendelse ifølge krav 1 eller 2, hvor dosen af acetylsalicylsyre er fra 1 mg til 75 mg.

4. Acetylsalicylsyre til anvendelse ifølge krav 1 eller 2, hvor dosen af acetylsalicylsyre er fra 2 mg til 60 mg.

5. Acetylsalicylsyre til anvendelse ifølge krav 1 eller 2, hvor dosen af acetylsalicylsyre er fra 5 mg til 40 mg.

6. Acetylsalicylsyre til anvendelse ifølge krav 1 eller 2, hvor dosen af acetylsalicylsyre er fra 10 mg til 30 mg.

7. Acetylsalicylsyre til anvendelse ifølge krav 1 eller 2, hvor dosen af acetylsalicylsyre er fra 12 mg til 25 mg.

8. Acetylsalicylsyre til anvendelse ifølge krav 1 eller 2, hvor dosen af acetylsalicylsyre er fra 15 mg til 20 mg.

9. Acetylsalicylsyre til anvendelse ifølge et hvilket som helst af de foregående krav, hvor dosen administreres som en indledende behandling som reaktion på et symptom på en tromboembolisk hændelse.

DRAWINGS

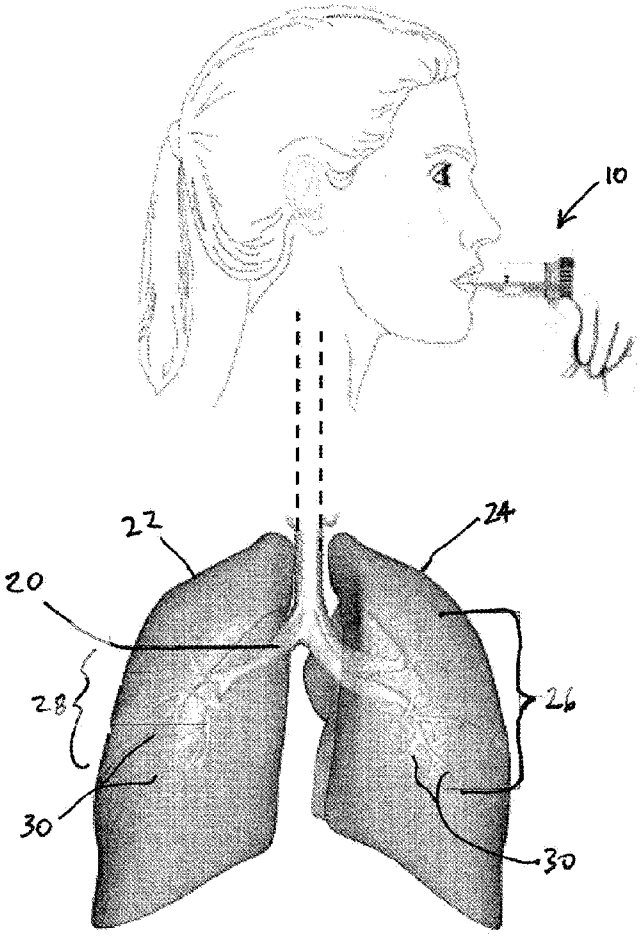

FIG. 1

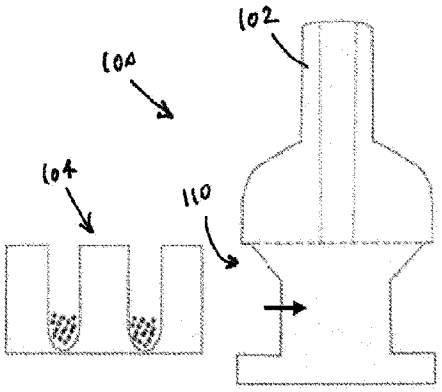

FIG. 2A

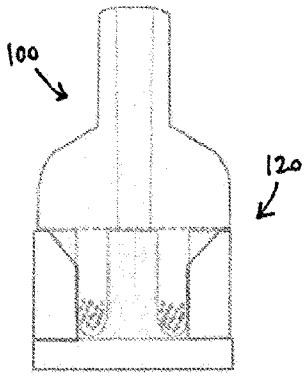

FIG. 2B

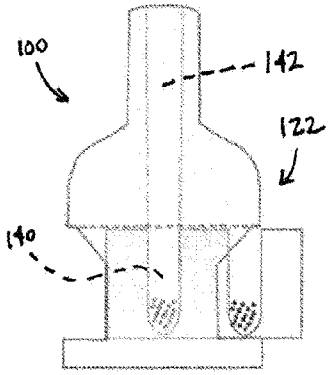

FIG. 2C

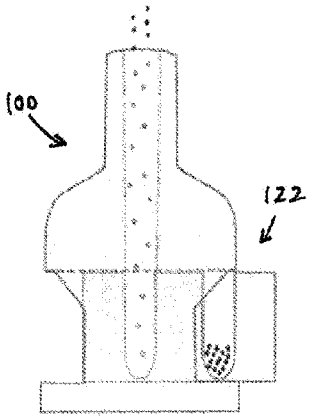

FIG. 2D

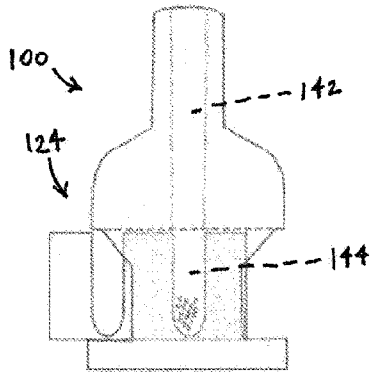

FIG. 2E

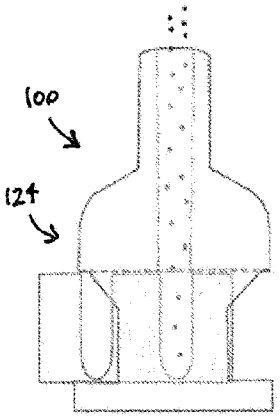

FIG. 2F