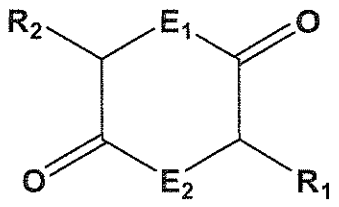
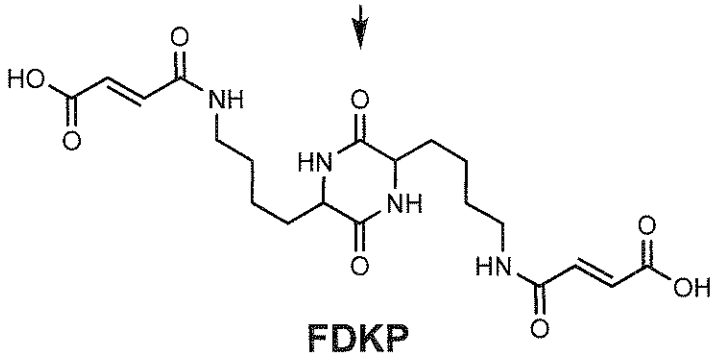
diketopiperazines are represented by the compound of the general Formula 1 as shown below where E=N. One or both of the nitrogens can be replaced with oxygen to create the substitution analogs diketomorpholine and diketodioxane, respectively.



Formula 1

[000198] These 2,5 diketopiperazines have been shown to be useful in drug delivery, particularly those bearing acidic R groups (see for example U.S. Patent Nos. 5,352,461 entitled "Self Assembling Diketopiperazine Drug Delivery System;" 5,503,852 entitled "Method For Making Self-Assembling Diketopiperazine Drug Delivery System;" 6,071,497 entitled "Microparticles For Lung Delivery Comprising Diketopiperazine;" and 6,331,318 entitled "Carbon-Substituted Diketopiperazine Delivery System," each of which is incorporated herein by reference in its entirety for all that it teaches regarding diketopiperazines and diketopiperazine-mediated drug delivery). Diketopiperazines can be formed into drug adsorbing microparticles. This combination of a drug and a diketopiperazine can impart improved drug stability and/or absorption characteristics. These microparticles can be administered by various routes of administration. As dry powders these microparticles can be delivered by inhalation to specific areas of the respiratory system, including the lung.

[0001] The fumaryl diketopiperazine (3,6-bis(N-fumaryl-4-aminobutyl)-2,5-diketopiperazine; FDKP) is one preferred diketopiperazine for pulmonary applications:



FDKP

flowability so that larger particles (for example on the order of 100 microns) can have reasonable flowability despite somewhat elevated rugosity. However for particles useful for delivery into the deep lung, such as those with primary particle diameters of 1-3 microns, even modestly elevated rugosity or 2-6 may be cohesive. Highly cohesive powders can have rugosities ≥10 (see example A below).

[000213] Many of the examples below involve the use of dry powders comprising fumaryl diketopiperazine (3,6-bis(N-fumaryl-4-aminobutyl)-2,5-diketopiperazine; FDKP). The component microparticles are self-assembled aggregates of crystalline plates. Powders comprised of particles with plate-like surfaces are known to have generally poor flowability, that is, they are cohesive. Indeed smooth spherical particles generally have the best flowability, with flowability generally decreasing as the particles become oblong, have sharp edges, become substantially two dimensional and irregularly shaped, have irregular interlocking shapes, or are fibrous. While not wanting to be bound, it is the applicants' present understanding that the crystalline plates of the FDKP microparticles can interleave and interlock contributing to the cohesiveness (the inverse of flowability) of bulk powders comprising them and additionally making the powder more difficult to deagglomerate than less cohesive powders. Moreover factors affecting the structure of the particles can have effects on aerodynamic performance. It has been observed that as specific surface area of the particles increases past a threshold value their aerodynamic performance, measured as respirable fraction, tends to decrease. Additionally FDKP has two chiral carbon atoms in the piperazine ring, so that the N-fumaryl-4-aminobutyl arms can be in cis or trans configurations with respect to the plane of the ring. It has been observed that as the trans-cis ratio of the FDKP used in making the microparticles departs from an optimal range including the racemic mixture respirable fraction is decreased and at greater departures from the preferred range the morphology of the particles in SEM becomes visibly different. Thus embodiments of the invention include systems of the device plus DKP powders with specific surface areas within preferred ranges, and the device plus FDKP powders with trans-cis isomer ratios within preferred ranges.

[000214] FDKP microparticles either unmodified or loaded with a drug, for example insulin, constitute highly cohesive powders. FDKP microparticles have been

[000228] In still yet a further embodiment, a method of treating obesity, hyperglycemia, insulin resistance, and/or diabetes is disclosed. The method comprises the administration of an inhalable dry powder composition or formulation comprising a diketopiperazine having the formula 3,6-di(N-X-4-aminobutyl)-2,5-diketopiperazine, wherein X is selected from the group consisting of succinyl, glutaryl, maleyl, and fumaryl. In this embodiment, the dry powder composition can comprise a diketopiperazine salt. In still yet another embodiment of the present invention, there is provided a dry powder composition or formulation, wherein the diketopiperazine is 3,6-di(N-fumaryl-4-aminobutyl)-2,5-diketopiperazine, with or without a pharmaceutically acceptable carrier, or excipient.

[000229] An inhalation system for delivering a dry powder formulation to a patient's lung, comprising a dry powder inhaler configured to have flow conduits with a total resistance to flow in a dosing configuration ranging in value from 0.065 to about 0.200 (√kPa)/liter per minute.

[000230] In one embodiment, a dry powder inhalation kit is provided comprising a dry powder inhaler as described above, one or more medicament cartridge comprising a dry powder formulation for treating a disorder or disease such as respiratory tract disease, diabetes and obesity.

EXAMPLE 1

[000231] **Measuring the resistance and flow distribution of a dry powder inhaler – cartridge system**: Several dry powder inhaler designs were tested to measure their resistance to flow – an important characteristic of inhalers. Inhalers exhibiting high resistance require a greater pressure drop to yield the same flow rate as lower resistance inhalers. Briefly, to measure the resistance of each inhaler and cartridge system, various flow rates are applied to the inhaler and the resulting pressures across the inhaler are measured. These measurements can be achieved by utilizing a vacuum pump attached to the mouthpiece of the inhaler, to supply the pressure drop, and a flow controller and pressure meter to change the flow and record the resulting pressure. According to the Bernoulli principle, when the square root of the pressure drop is plotted versus the flow rate, the resistance of the inhaler is the slope of the linear portion of the curve. In these experiments, the resistance of the inhalation system, comprising a dry powder inhaler and cartridge as described herein, were measured in the dosing configuration using a resistance measuring