To enable aerosolized particles to settle in the targeted regions of the lung associated with local and/or systemic drug delivery, the particle size must be carefully considered. In general, one of the main factors which determines the average particle size of a powdered composition is the selection of a suitable process from existing powder technologies. In addition, if the cohesive forces (which are dependent on the size of particles) acting on the powder are pronounced, the designed shear of a provided airflow may not be sufficient to separate an included drug from the carrier particles, and will subsequently result in low deposition efficiencies within the targeted areas of the pulmonary system.

In general, particles which are of an aerodynamic diameter greater than 5 μm generally tend to be deposited within the mouth or throat, and therefore offer little therapeutic benefit to a patient. In contrast, particles having an aerodynamic diameter smaller than 0.5 μm generally do not settle out of a provided air flow to stay deposited in the lungs, and may undesirably be exhaled by a patient administered such a formulation.

There is therefore a need to provide formulations which are better designed for inhalation that overcome, or at least ameliorate, one or more of the disadvantages of existing inhaled-formulations as described above.

Summary

~~According to a first aspect, t~~There is provided a dry powder formulation comprising a combination of at least a first pharmaceutically active quinolone and a second pharmaceutically active quinolone.

In a first aspect, there is provided a dry powder formulation comprising a combination of at least a first

pharmaceutically active quinolone and a second pharmaceutically active quinolone at a ratio of at least 1:2.

Advantageously, the combination of the first and second pharmaceutically active quinolones may be a synergistic combination. Hence, the dry powder formulation

may be more effective against an infection as compared to just the mere sum of the anti-infective effects of the two quinolones when used separately. Having a synergistic combination of the two quinolones may broaden the antimicrobial spectrum and may aid in preventing the emergence/re-emergence of resistant microbes such as bacteria. The synergistic combination of the two quinolones may lower the dose of the individual quinolones, leading to a reduction in the side effects and the treatment costs.

The dry powder formulation may be administered via a dry power inhaler. The dry powder formulation may not require administration via a nebulizer and hence may not be present in an aerosol form from a solution or suspension. Due to the use of an inhaler as compared to a nebulizer, a higher fine particle fraction of the powdered quinolones may be administered as compared to that achievable by a nebulizer (which is about 10% or less). In addition, the dry powder inhaler can be used to administer the drug combination without any substantial clogging of the inhaler, unlike when using a nebulizer to co-nebulize two drugs as there is a risk that the quinolones may precipitate in solution and clog the nebulizer. Further, the dry powder formulation may be more stable as compared to a quinolone solution or suspension since the quinolones are present as powdered particles. Due to the greater stability of the dry powder formulation, the formulation can be stored for a longer period of time.

The dry powder formulation may be a combination of only the first and second pharmaceutically active quinolones and may not require the addition of a third fluoroquinolone. However, the dry powder formulation may contain additional active ingredients that are not quinolones and which may have a beneficial medical effect

on a patient. The additional active ingredient may be a mucolytic and/or anti-inflammatory agent(s).

~~According to a second aspect, t~~There is provided a method for preparing a dry powder formulation comprising the step of forming particles of at least a first pharmaceutically active quinolone and a second pharmaceutically active quinolone.

According to a second aspect, there is provided a method for preparing a dry powder formulation comprising the step of forming particles of at least a first pharmaceutically active quinolone and a second pharmaceutically active quinolone at a ratio of at least 1:2.

~~According to a third aspect, t~~There is provided a dry powder inhaler comprising a dry powder formulation having a combination of at least a first pharmaceutically active quinolone and a second pharmaceutically active quinolone.

According to a third aspect, there is provided a dry powder inhaler comprising a dry powder formulation having a combination of at least a first pharmaceutically active quinolone and a second pharmaceutically active quinolone at a ratio of at least 1:2.

The dry powder inhaler may be portable and easy to use. Hence, the use of the dry powder inhaler to administer the dry powder formulation may enhance patient compliance.

According to a fourth aspect, there is provided a dry powder formulation as defined above for use in therapy.

According to a fifth aspect, there is provided a dry powder formulation as defined above for use in treating a bacterial infection in a patient.

According to a sixth aspect, there is provided use of the dry powder formulation as defined above in the

manufacture of a medicament for the treatment of a bacterial infection in a patient.

Definitions

The following words and terms used herein shall have the meaning indicated:

The term "dry powder formulation" refers to a formulation that contains finely dispersed solid particles having a certain particle size distribution that are capable of (i) being readily dispersed in or by means of an inhaler and (ii) be administered to a subject via inhalation so that a portion of the particles reach the

Claims

1. A dry powder formulation comprising a combination of at least a first pharmaceutically active quinolone and a second pharmaceutically active quinolone at a ratio of at least 1:2.

~~2. The dry powder formulation of claim 1, wherein said ratio is selected to provide a synergistic effect on a microbial infection.~~

~~3.~~2. The dry powder formulation of claim 1~~ or 2~~, wherein said first pharmaceutically active quinolone and said second pharmaceutically active quinolone is independently selected from a fluoroquinolone.

~~4.~~3. The dry powder formulation of ~~any one of the preceding~~ claim~~s~~ 2, wherein said fluoroquinolone is selected from the group consisting of ciprofloxacin, gatifloxacin, enoxacin, fleroxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pefloxacin, rufloxacin, balofloxacin, grepafloxacin, levofloxacin, pazufloxacin, sparfloxacin, temafloxacin, tosufloxacin, clinafloxacin, gemifloxacin, moxifloxacin, sitafloxacin, trovafloxacin, prulifloxacin and pharmaceutically acceptable salts thereof.

~~5.~~4. The dry powder formulation of claim ~~4~~3, wherein said first pharmaceutically active quinolone is

ciprofloxacin and said second pharmaceutically active quinolone is gatifloxacin.

~~6.~~5. The dry powder formulation of claim ~~5~~4, wherein said first pharmaceutically active quinolone is ciprofloxacin hydrochloride and said second pharmaceutically active quinolone is gatifloxacin hydrochloride.

~~7.~~6. The dry powder formulation of any one of the preceding claims, wherein said first pharmaceutically active quinolone and said second pharmaceutically active quinolone are present in said formulation in the form of particles having a narrow particle size distribution.

~~8.~~7. The dry powder formulation of claim ~~7~~6, wherein said particles have a particle size between 500 nm to 4 μm.

~~9.~~8. The dry powder formulation of claim ~~7~~6 or ~~8~~7 wherein said particles have a mono-modal size distribution with a span $(D_{90}-D_{10})/D_{50}$ of 0.5 to 2.

~~10.~~9. The dry powder formulation of any one of claims 8 to 10, wherein said particles have a fine particle fraction in the range of 1% to 99%.

~~11.~~10. The dry powder formulation of any one of the preceding claims, further comprising at least one excipient.

~~12.~~11. The dry powder formulation of any one of the preceding claims, further comprising at least one mucolytic agent.

~~13.~~12. The dry powder formulation of any one of the preceding claims, wherein said dry powder formulation is for administration via a dry powder inhaler.

~~14.~~13. A method for preparing a dry powder formulation comprising the step of forming particles of at least a first pharmaceutically active quinolone and a second pharmaceutically active quinolone at a ratio of at least 1:2.

~~15.~~14. The method of claim ~~14~~13, wherein said forming step comprises the step of co-spray drying a binary system of aqueous solutions of said first pharmaceutically active quinolone and said second pharmaceutically active quinolone.

~~16.~~15. The method of claim ~~15~~14, wherein said aqueous solutions are provided at a weight ratio of at least 1:2.

~~17.~~16. The method of claim ~~16~~15, wherein said aqueous solutions are aqueous solutions of ciprofloxacin hydrochloride and gatifloxacin hydrochloride that are provided at a weight ratio of 1:2.5.

~~18.~~17. A dry powder inhaler comprising a dry powder formulation having a combination of at least a first pharmaceutically active quinolone and a second pharmaceutically active quinolone at a ratio of at least 1:2.

~~19.~~18. The dry powder inhaler of claim ~~18~~17, wherein said dry powder inhaler disperses said dry powder formulation at a rate between 30 to 100 L/min.

~~20.~~19. The dry powder formulation of any one of claims 1 to ~~13~~12 for use in therapy.

~~21.~~20. The dry powder formulation of any one of claims 1 to ~~13~~12 for use in treating a bacterial infection in a patient.

~~22.~~21. The dry powder formulation of claim ~~21~~20, wherein said infection is caused by a bacteria having a genera selected from the group consisting of *Pseudomonas*, *Escherichia*, *Haemophilus*, *Klebsiella*, *Legionella* , *Moraxella*, *Proteus*, *Acinetobacter*, *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Mycobacterium*, *Corynebacterium* and *Mycoplasma*.

~~23.~~22. The dry powder formulation of claim ~~22~~21, wherein said infection is caused by a bacteria selected from the group consisting of *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Proteus mirabilis*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphyloccus aureus*, *Streptococcus pneumoniae*, *Staphylococcus epidermis*, *Eterococcus faecalis*, and *Streptococcus pyogenes*, *Mycobacterium tuberculosis*, non-tuberculous *mycobacteria*, *Corynebacterium diphtheria* and *Mycoplasma pneumoniae*.

~~24.~~23. Use of the dry powder formulation of any one of claims 1 to ~~13~~12 in the manufacture of a medicament for the treatment of a bacterial infection in a patient.

~~25.~~24. Use of claim ~~24~~23, wherein said bacterial infection is selected from the group consisting of pharyngitis, epiglottitis, laryngitis tracheitis, bronchitis, bronshiolitis, pneumonia and tuberculosis.

~~26.~~25. Use of claim ~~24~~ 23 or ~~25~~24, wherein said patient is suffering from chronic obstructive pulmonary disease, cystic fibrosis or asthma.