Respirable microparticles of aminoglycoside antibiotics for lung infections in cystic fibrosis patients

WHO WE ARE

PlumeStars, Italian innovative start-up company, laid its foundation from Biopharmanet-TEC, the Interdipartimental Center of the University of Parma, in September 2013. Plumestars leverages on its strong technological know-how to design and develop dry powders for inhalation and orphan medicines designation. Plumestars holds a patented technology claiming the molecular deposition of fatty acids on drug microparticles applicable to several drugs.

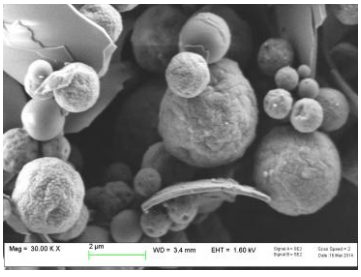
The founders of PlumeStars, Paolo Colombo (CEO), Anna Giulia Balducci, Francesca Buttini and Ruggero Bettini, are four scientists that share the same passion for science and technology. In the Advisory Board, Fabio Borella, is the mentor of PlumeStars.

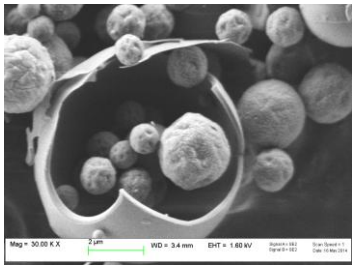
WHAT WE DO

Pulmonary administration of antibiotic drugs, as powder for inhalation, are an alternative to administration by nebulization. Very highly respirable microparticulate powders with high content of aminoglycoside drugs have been prepared by spray drying of drug solutions containing sodium stearate. The novel dried powders for inhalation are aerosolized using a high-dose dry powder inhaler.

DESCRIPTION OF THE PRODUCT

For the optimal lung deposition of an inhalation powder, the particles must have a volume, density and shape useful for producing a stable aerosol with the air turbulence created by the inhalation act through the inhaler. Then, the aerodynamic behavior is the crucial aspect of a powder for inhalation, since it expresses the capability of a particle to fly in an air stream. In inhalation, this is recognized as aerosol respirability and it is measured by the aerodynamic diameter of particles.





The aerodynamic assessment of a powder for inhalation is essential for the definition of the dose to inhale. The amount of drug loaded in the capsule/device is the labeled dose. Generally, the dose emitted from the device, when patient inhales through it, is lower. However, the dose relevant for the activity is the amount of drug deposited in the lung, known as fine particle dose. This is the critical value to assess and corresponds to the mass of particles in the aerosol having aerodynamic size lower than 5 µm.

Plumestars S.r.l. | Strada Inzani 1, 43125 - Parma

Tel. 320 4344670 - info@plumestars.com

Comparing the three mentioned doses, it is quite common that the amount of drug reaching the lung epithelium, thus exerting its activity, is less than 20% of the labeled dose. As a consequence, powders for inhalation require engineered particles for being efficient. An optimized formulation is characterized by a powder functional to be metered (labeled dose), aerosolized (emitted dose) and efficiently transported into lung (fine particle dose).
In Tobramycin and Amikacin inhalation powders, a proprietary spray drying technology was used to construct the powder to inhale having high content of amikacin. The powders are constituted by particles of very small aerodynamic diameter, low density and favorable shape for aerosolization. In particular, the aminoglycoside antibiotics powders for inhalation has been fabricated with a minimal amount of excipients (1% w/w of sodium stearate) allowing to straiten the mass of powder to meter for the labeled dose; at the same time, compared to existing methods, higher dose of active principle in the lungs (fine particle dose) is provided with very low amount of excipients.

The development of antibiotics inhalation powders started from the consideration that the substance in solid state could be protected from humidity. The powder was manufactured accordingly to the patented technology platform on which the startup company PlumeStars has been founded. The patent claims the preparation of antibiotic microparticles whose respirability is enhanced by the small amount of sodium stearate deposited on particle surface.
The sponsor technology consists in introducing 1% w/w of sodium stearate as hydrophobic adjunct dispersed in the drug solution to be spray dried. The surface activity of sodium stearate, dissolved in the solution to spray drying, moves the molecules at air/liquid interface of sprayed droplets. Therefore, during droplet drying, the molecules of stearate concentrate on the surface of the obtained particles. This molecular coating protects the amikacin from the environmental humidity, keeps very high the drug content of the particle and elevates the aerosolization properties.

MAIN ADVANTAGES

The lung infection therapy conducted by inhalation tackles the pathogen microorganisms at the site of infection at the same time limiting the adverse effects of systemic medication. An inhalation powder facilitates the administration compared to nebulization which requires complex instruments, more time and care efforts. Dry powder inhalation technology involves a simple breath through hand able devices which do not need electricity. The administration can be carried out everywhere with less drug than nebulization. The drug works where it is needed, without affecting healthy organs. The innovation is a novel medicinal product of aminoglycoside powder for inhalation for the management of Pseudomonas pulmonary infections in CF patients. The aim is to prevent exacerbations or to manage them without hospitalization. The administration of inhalation powder simplifies the therapy, reduces the dose and improves the local activity. The innovation of the new product is to offer a valid alternative to the other antibiotics for inhalation, keeping as low as possible the amount of powder to be inhaled by the patient while maximizing the amount of active ingredient deposited in the lung. In the medicinal product, the amikacin powder inhaled, due to the high amikacin content and powder respirability, concentrates more antibiotic in contact with the lung infected areas.

TECHNOLOGY KEY WORDS

Pharmaceutical products, Drugs, Antibiotics, Drug delivery, Human Health activities

CURRENT STAGE OF DEVELOPMENT

In vitro data allowed to obtain the orphan drug designation from EMA and FDA for amikacin powder for inhalation. Tobramycin application could be applied for designation as well, provided to show minimal *in vivo* data versus the registered tobramycin DPI, demonstrating a superiority in convenience and compliance.

TECHNICAL AND SCIENTIFIC PUBLICATIONS

Pulmonary Spray Dried Powders of Tobramycin Containing Sodium Stearate to Improve Aerosolization Efficiency, C. PARLATI, P. COLOMBO, F. BUTTINI, P. YOUNG, H. ADI, A.J. AMMIT, D. TRAINI, Pharmaceutical Research, Vol.26, May 2009, 1084-1092

BELOTTI S., ROSSI A., COLOMBO P, BETTINI R, REKKAS D, POLITIS S, COLOMBO G, BALDUCCI AG, BUTTINI F. Spray dried amikacin powder for inhalation in cystic fibrosis patients: A quality by design approach for product construction. International Journal of Pharmaceutics 471 (2014) 507–515