

The aim of the present PhD project was to design inhalable powder-based formulations for pharmaceutical products that may improve the treatment of pulmonary diseases, mainly cystic fibrosis, and may be easier for patients to use. Particularly, the present project aims to supply CF patients with flavonoids (Naringin) and aminoglycosides (Gentamicin sulfate) in a respirable form as a valid alternative over more conventional (oral or parenteral) anti-inflammatory and antibiotic therapy. As a matter of fact, in CF epithelial cells, antioxidant defense systems appear to be defective in their ability to control the amount of ROS produced and over abundance of ROS may cause tissue injury-events and modify intracellular signalling pathways leading to enhanced inflammatory processes, typical of CF airways. Overall, evidence suggests improved CFTR function *in vitro* when flavonoids, such as genistein, are used. For chronic *Pseudomonas aeruginosa* (*Pa*) infections in CF, gentamicin given by pulmonary route may play an important role.

In fact, it was observed that daily inhalation of some aminoglycosides from nebulized solution delays the acquisition of chronic *Pa* infections and decreases CF progression.

The project addresses a number of the key features that are outstanding in inhaled delivery, mainly - characteristic of the active drug; - properties of the drug formulation, particularly powder flow, particle size, shape, surface properties and drug/carrier interaction; - consistent dose delivery and high proportion of dose getting to the lung; - performance of the inhaler device, including aerosol generation and delivery. A balance among these characteristics is necessary in the design of a drug formulation intended for pulmonary administration.

Utilizing proven (Spray-drying) or innovative (Supercritical Assisted Atomization) technology, stable and micronized powders useful for dry powder inhaler (DPI) production have been developed. Moreover, the research has been based on *in vitro* product test methods to evaluate the health effects of produced powders and their aerodynamic behaviour through the pulmonary system. Optimized stability and bioavailability of the selected drugs, the achieving of therapeutically effective concentrations for the pulmonary care of cystic fibrosis have been other goals of the research. Technologies and products that the research is aimed to develop would be of interest to a number of pharmaceutical companies either in the respiratory area or trying to get a foothold in this market.

Specific objectives of this research have been:

- design and development of Dry Powder Inhalers (DPIs) containing flavonoids (Naringin) or aminoglycoside antibiotics (Gentamicin sulfate) micronized powder by spray drying production or by Supercritical Assisted Atomization (SAA);

- optimization of the aerodynamic characteristics of the powders, through the use of excipients (amino acids) not toxic for lung but able to improve the powder flow properties and dispersion which, in turn, may increase lung deposition of the drugs;
- *in vitro* evaluation of the biological activity of the engineered particles on a model of bronchial epithelial cell lines from patients with cystic fibrosis (CuFi1, F508del/F508del CFTR), in comparison to the activity of the same products on normal bronchial epithelial cell lines (NuLi1).