



Carrier optimization of pulmonary powder systems with using computational intelligence tools

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ABSTRACT

Efficient delivery of drug particles to the respiratory tract determines therapeutic efficiency of pulmonary drugs. Only particles with an aerodynamic diameter (d_{ae}) below five micrometers (μm) deposit in deep lungs. However fine particles, because of their cohesive nature, frequently cause difficulties related to the manufacturing process and stability of the product. This study is focused on the optimization of carriers for pulmonary drug delivery systems with the use of empirical models. Advanced computational intelligence tools were applied to produce a mathematical formula able to predict fine particle fraction (FPF) for a particular formulation. FPF is a mass percentage of drug particles with an aerodynamic diameter below $5 \mu\text{m}$. The best model was characterized by normalized root mean squared error (NRMSE) below 8% and $R^2 = 0.85$. The goal of the *in silico* optimization was to find the possible directions of carrier modification in order to maximize FPF. Obtained results were applied to the laboratory experiments and resulted in the two new formulations with bovine serum albumin (BSA) as a model drug. Experimental results confirmed the model predictions, and the formulation composed of the carrier with higher bulk density and surface skewness resulted in greater FPF value. The presented work is an example of computational intelligence tools implementation and particles surface assessment based on SEM images in design of the decision support systems for the development of pulmonary powder formulations.

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1. Introduction

Pulmonary drug delivery systems allow the administration of active pharmaceutical ingredient (API) directly to the respiratory system causing a local or systemic therapeutic effect. Pulmonary drugs are applied in the treatment of various diseases like asthma and chronic obstructive pulmonary disease, cystic fibrosis or diabetes. Dry powder inhalers (DPI) produce aerosol from powder formulation and are especially attractive concerning the administration of labile compounds like peptides and proteins [1,2]. Efficient API delivery to the respiratory system is crucial for effective treatment. Particles deposition depends on many factors related to formulation (particles' size, shape and density), inhaler device and patient compliance. Assessment of particles behavior in the air stream is a standard procedure during the pulmonary formulation development. It is performed in impactors and as a result fine particle fraction (FPF) is obtained, which is a mass percentage of drug particles with an aerodynamic diameter below $5 \mu\text{m}$. It was found that particles, with aerodynamic diameter (d_{ae}) below five μm , deposit in deep lungs [3]. However such particles usually exhibit poor flowability and tend to agglomerate due to their highly cohesive nature [5–7].

The addition of carrier particles modifies the behavior of the mixture. Drug particles tend to attach to the carrier surface, which reduces the agglomeration problem. During the inhalation particles detach from each other and the proper quality aerosol is produced. The design of the carriers is significant for proper formulation development. Extensive studies have confirmed the effects of carrier particle size, density, shape and surface roughness on the particles deposition [8]. A better understanding of factors influencing pulmonary powder systems behavior during inhalation is an object of laboratory experiments and computer simulations. Tong et al. applied discrete element modeling (DEM) coupled with computational fluid dynamics (CFD) method to simulate drug particles detachment from carriers during wall impaction [9]. It was assessed that the impact of particles size, impact angle, and velocity influence the aerosol behavior. Authors also proposed the mathematical formula for FPF prediction based on *in silico* simulation results. All experiments were performed with an assumption of the spherical shape of drug and carrier particles. A further example is work of Vinchurkar et al., where CFD method was applied to simulate *in vitro* deposition of powder systems without carriers [10]. The authors constructed a virtual 3D model of Mark II Andersen cascade impactor and performed computational experiments to assess the influence of particles charge on their aerodynamic properties. Authors assumed a spherical shape of particles during experiments. In mentioned works,

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authors examined factors influencing interparticle interaction and their impact on formulation performance during inhalation. There are still factors like e.g. particles surface, which was not taken into account in previous works.

Development of pulmonary powder formulation is currently carried out mostly with trial-and-error approach. Therefore, from both scientific and regulatory perspectives, there is an increasing need for a deeper process understanding toward pharmaceutical drug development and manufacturing. Recent guidelines provided by FDA like Process Analytical Technology (PAT) Guidance [11] or ICH guidelines [12] are reflections of that need. According to the above guidelines in-depth process understanding leads to a development of safe, efficient and high-quality pharmaceutical products. From such point of view, computational intelligence (CI) tools are interesting solution due to the ability to self-adaptation to data and it allows for automatic analysis of complex, non-linear and multi-dimensional problems. CI was successfully applied in pharmaceutical technology to build predictive models for macromolecules dissolution from microparticles [13], particles size [14], granules size after milling process [15], tablet properties [16], and pulmonary powder systems performance [17]. The data-driven modeling approach was also presented as a method for expert systems construction in formulation development process [18].

The current study shows the concept of pulmonary carrier based formulation optimization using empirical models. The development of high-quality predictive model was based on advanced CI tools, namely artificial neural networks, decision trees and evolutionary computations. The empirical model introduced in the article allows calculating FPF value for carrier-based pulmonary powder system based on six variables, where three of them represent carrier surface derived from SEM photographs. Additionally, the model takes into account bulk density of the carrier particles, air flow rate during *in vitro* assay and drug particles content in the formulation. The model was applied to evaluate the influence of individual variables on predicted FPF value and it was also used in optimization tasks.

2. Materials and methods

2.1. Data set

The database was prepared based on experimental results provided by School of Chemical and Biomedical Engineering in Singapore. It contained 26 records for different formulations composed of 6 different hydroxyapatite (HA) pollen-shape carriers mixed with budesonide as a model drug in various ratios. The HA carriers had an average size range of 15.1–45.9 μm and the budesonide particles had an average size of $2.5 \pm 1.1 \mu\text{m}$. More thorough description of HA particles and budesonide can be found in Hassan and Lau [19–21]. Particles deposition was assessed in Andersen Cascade Impactor (ACI, COPLEY Scientific) at two different air flow rates: 30 and 60 L/min with Rotahaler® as an inhaler device. Drug carriers were obtained with proper control of size, density and surface characteristic. Experimental results included in the database were enriched by the properties of the surface roughness based on SEM photographs. The database contained 17 input variables describing: surface, density, geometric size of the carrier particles, air flow rate during the deposition study and quantitative composition of the formulation (Table 1). Fine particle fraction (FPF) was the only dependent variable. All constructed models were of multiple input single output type (MISO). Before models building, the database was divided according to the extended k-fold cross validation methodology, where a single fold included all the experiments for single carrier particle. The data split mimics the conditions of model testing similar to its practical use, where the model is used as a support tool for pulmonary drugs development regarding searching for new carriers.

Table 1
Structure of the database.

	Variable name	Variable group
In1	Rq - root mean square deviation	Carrier particles surface characteristic based on SEM photographs
In2	Ra - arithmetical mean deviation	
In3	Rsk - skewness of the assessed profile	Carrier particles geometrical size
In4	Rku - kurtosis of the assessed profile	
In5	Rv - lowest valley	Carrier particles density
In6	Rp - highest peak	
In7	Rt - the total height of the profile	<i>In vitro</i> deposition conditions
In8	FPO - mean polar facet orientation, given in degrees	
In9	MFOV - variation of the polar facet orientation, given in degrees	Quantitative composition of powder systems
In10	FAD - direction of azimuthal facets, given in degrees	
In11	MRV - mean resultant vector	Deposition <i>in vitro</i>
In12	SA - surface area	
In13	Particle average size [μm]	
In14	Bulk density [g/cm^3]	
In15	Tap density [g/cm^3]	
In16	Flow rate [L/min]	
In17	Drug content [m/m%]	
Output	FPF - fine particles fraction	

2.2. Carriers surface analysis

The surface of the objects can be analyzed based on images from scanning electron microscope (SEM) [22]. In current study, assessment of carriers surface was conducted using SurfCharJ [23] plugin for ImageJ (v. 1.47n) [24], which enables surface roughness quantification. Before the analysis, each picture was standardized regarding metric scale and its deep (32-bit grayscale). Ten randomly chosen square sectors with size 10 μm by 10 μm of the particle surface were analyzed. All surface roughness parameters were calculated with standard settings of SurfCharJ plugin with an additional “level surface” option, which allows adjustment of the surface by subtracting a regression plane from the surface. Based on SEM images 13 variables describing surface properties were calculated, namely: arithmetical mean deviation (Ra), root mean square deviation (Rq), skewness of the assessed profile (Rsk), kurtosis of the assessed profile (Rku), lowest valley (Rv), highest peak (Rp), the total height of the profile (Rt), average height of an unlevelled surface (Rc), mean polar facet orientation (FPO), variation of the polar facet orientation (MFOV), direction of azimuthal facets (FAD), mean resultant vector (MRV) and surface area (SA). Surface descriptors included in the database were the average of 10 samples.

2.3. Model assessment

Models' goodness of fit was expressed as root-mean-squared error RMSE (Eq. 1), normalized root-mean-squared error NRMSE (Eq. 2) and determination coefficient R^2 (Eq. 3) between predicted and experimental values. Normalized root-mean-square error (NRMSE) values were calculated according to experimental FPF range (4.9–42.3%) within the range in data set.

$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^n (\text{pred}_i - \text{obs}_i)^2}{n}} \quad (1)$$

where: obs_i , pred_i = observed and predicted values respectively, i = data record number, n = total number of records.

$$\text{NRMSE} = \frac{\text{RMSE}}{X_{\max} - X_{\min}} \cdot 100\% \quad (2)$$

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