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Evaluation of carrier size and surface morphology in carrier-based dry powder inhalation by surrogate modeling

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HIGHLIGHTS

- Drug carrier design parameters were evaluated using surrogate modeling.
- Image analysis tool was used for surface roughness determination from SEM images.
- Important carrier design parameters were identified and models were formulated.
- Optimization were performed to provide insights to high fine particle fractions.

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ABSTRACT

In this work, design parameters of carrier-based dry powder inhalation were studied using surrogate modeling technique. The surrogate models constructed were then used to evaluate the key design parameters independently, which were otherwise difficult to determine based on experimental studies alone. Artificial neural network (ANN) was chosen as the surrogate modeling technique and models were constructed based on experimental data obtained from the literature. Twenty-eight variables describing the carrier size distribution, density, surface characteristics and operating conditions of dry powder inhaler were used as the input variables and emitted dose (ED) and fine particle fraction (FPF) were used as the output variables. Carrier surface characteristics were evaluated by applying image analysis on carrier SEM images. Genetic algorithm (GA) was used for the selection of important variables to be included in the surrogate models. Sensitivity analysis was also performed to determine the key variables affecting ED and FPF. Key design criteria for carrier-based dry powder inhalation were proposed based on the surrogate models constructed.

1. Introduction

One of the aerosol-generating devices used for inhaled drug delivery is dry powder inhaler (DPI). DPI consists of micronized drug particles, which are inhaled as a cloud with or without the aid of carrier particles (Adi et al., 2008; Martini et al., 2000; Young et al., 2011). Drug particles having aerodynamic diameters between 2 and 4 μm were found to be ideal for deposition in the peripheral airway (Mitchell and Nagel, 2004; Stephenson and Thiel, 1980). However, particles in this size range are cohesive in nature that exhibit poor dispersibility (Hickey et al., 1994) and flowability (Byron, 1986). A mixture of the drug particles with large carrier particles 20–200 μm in size can enhance the dispersibility and flowability of the formulation that can lead to improved drug delivery efficiency (El-Gendy et al., 2012; Larhrib et al., 1999; Le et al., 2012; Rahimpour and Hamishehkar, 2012; Tan et al., 2015; Timsina et al., 1994; Zhou and Morton, 2012).

In vitro aerosolization performance and drug delivery efficiency of a DPI is generally represented by emitted dose (ED) and fine particle fraction (FPF) (Kumon et al., 2008; Tan et al., 2015). ED represents the powder flow behavior while FPF characterizes the aerosolization behavior of the drug particles. Parameters such as inhalation flow rate and carrier-to-drug mixing ratio that affect ED and FPF are typically well studied and reported in the literature. An increase in the inhalation flow rate increases both the ED and FPF (Kou et al., 2012; Zeng et al., 2000a). An increase in carrier-to-drug mixing ratio was reported to decrease the FPF until a

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carrier-to-drug mixing ratio of 20:1, beyond which a further increase in carrier-to-drug mixing ratio increases the FPF (Adi et al., 2007; Harjunen et al., 2003; Hassan and Lau, 2010b; Steckel and Müller, 1997).

The physical properties of the carriers such as particle size, shape, surface roughness, and other chemical properties of the carrier material have a significant impact on ED and FPF of carrier-based DPI (Concessio et al., 1999; Hickey and Concessio, 1997; Kou et al., 2012). However, findings reported in the literature for these factors are not conclusive. For example, FPF was reported to increase with a decrease in carrier particle size (Adi et al., 2007; Donovan and Smyth, 2010; Glover et al., 2008; Guenette et al., 2009; Karhu et al., 2000; Kou et al., 2012; Louey and Stewart, 2002; Louey et al., 2003; Podczeck, 1999; Steckel and Müller, 1997; Young et al., 2007; Zeng et al., 2000b). On the other hand, there are also findings showing FPF to increase with an increase in carrier particle size (Hassan and Lau, 2011; Podczeck, 1998). Information regarding the carrier particle size distribution is believed to play an important role in the behavior of ED and FPF. It was reported that the addition of a suitable amount of fine particles in the formulation is effective in enhancing FPF (Guchardi et al., 2008; Handoko et al., 2009; Louey and Stewart, 2002; Zeng et al., 1998, 2000b). Similarly, good FPF were demonstrated in carriers that have smooth surfaces (Kaialy and Nokhodchi, 2013; Maas et al., 2010) and carriers that have rough surfaces (Littringer et al., 2012). The impact of carrier surface roughness not only limits to the adhesion forces between drug and carrier particles (Podczeck, 1997, 1998), the scale of the carrier surface roughness can also affect the entrapment of drug particles on the carrier surface (Boshhiha and Urbanetz, 2009; Zhang et al., 2015). The relationship among the carrier properties, ED, and FPF, are highly complex and often interdependent. In a recent study, an empirical model was proposed to predict the FPF for carrier-based DPI by taking into account the contribution of carrier surface roughness (Pacławski et al., 2015). However, the understanding of the actual physical relationship between the carrier properties and FPF remains unclear.

This work aims to gain the understanding of important design parameters on dry powder inhalation efficiency on dry powder inhalation efficiency using surrogate modeling technique. Surrogate models allow a comprehensive understanding of complex behaviors among inter-related parameters, which are otherwise difficult to study experimentally (Agatonovic-Kustrin et al., 1998; Baumes et al., 2004; Chi et al., 2012; Hadjmohammadi and Kamel, 2008; Korany et al., 2012; Li et al., 2010; López et al., 2013; Nakayama et al., 2002; Palmer and Realff, 2002a,b; Shao et al., 2007; Tang et al., 2010; Yan et al., 2011a, 2012, 2011b). For example, the use of carrier particles of different sizes experimentally would typically involve different spread of the particle size distribution as well as different bulk and tap densities of the carrier particles. In the construction of surrogate models, in addition to standard parameters such as carrier average particle size, bulk and tap densities, inhalation flow rate, and carrier-to-drug mixing ratio, more detailed descriptive parameters such as the spread of the carrier particle size distribution, fine carrier fractions, and various descriptive parameters for carrier surface roughness were also considered. Therefore, it is necessary to explore the suitability of different parameters to describe the carrier surface roughness (Heng et al., 2000; Kawashima et al., 1998; Littringer et al., 2012). Genetic algorithm (GA), an evolutionary algorithm, is applied to select variables important for ANN models and to determine the ANN parameters. Sensitivity analysis was carried out to determine the relative importance of different parameters to ED and FPF. Key design criteria for carrier-based dry powder inhalation were proposed based on the surrogate models constructed.

2. Materials and methods

2.1. Dataset

All the carrier formulations and aerosolization properties used in this study were obtained from published literature using hydroxyapatite as carrier material (Hassan and Lau, 2010a,b, 2011; Nguyen et al., 2014). Budesonide drug particles having an average size of 2.5 ± 1.1 μm were used in all the studies. Parameters extracted include ED, FPF, flow rate, carrier-to-drug ratio, tap density, bulk density, Carr's compressibility index (CI), and carrier particle size distribution, represented by mean and variance of a fitted Gaussian distribution function. Some studies showed that the presence of fine carrier particles can improve DPI efficiency (Zeng et al., 2000a). Hence, the volume fractions of particles less than a certain size were also selected for investigation. In addition, various roughness parameters (Tan et al., 2015) of the carriers were also used since carrier surface roughness has both microscopic and macroscopic influence on the performance of DPI (Zhang et al., 2015). The determination of the roughness parameters will be described in Section 2.2. There are a total of 30 parameters considered in the study and a complete list of input and output variables is shown in Table 1. ED and FPF are the only two output parameters while the rest of the other 28 are input parameters containing information about the formulation such as carrier size, density, roughness variables, flowability, drug content, and inhalation flow rate.

2.2. Surface roughness analysis

Carrier surface roughness analysis were performed based on image analysis of SEM images using ImageJ® software (v2.33) (Abràmoff et al., 2004; Schneider et al., 2012) with SurfCharJ (v.1q) plugin (Chinga, 2003; Chinga et al., 2007). SEM images of carrier particles were converted to 32-bit grayscale format and rescaled to a standardized resolution of 20 pixels per micron. A square area of 200 pixels × 200 pixels in the center region of each carrier particle in the image was cropped for surface characterization by SurfCharJ (v.1q). Three cropped images were used to obtain an average value for each surface parameter for each carrier particle. Thirteen roughness parameters describing the surface properties were determined. Surface roughness parameters include root mean square deviation (Rq), arithmetical mean deviation (Ra), skewness of the assessed profile (Rsk), kurtosis of the assessed profile (Rku), lowest valley (Rv), highest peak (Rp), total height of the profile (Rt), average height of an unleveled surface (Rc), and surface orientation variables including 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).

2.3. Variables selection

It is a challenge to select the parameters needed to build an adequate surrogate model, especially when a large number of parameters are involved and the relative importance of the various input parameters on the output parameters are unknown. On the other hand, it is often not feasible to utilize all the available parameters because it can cause issues such as usage of irrelevant parameters, overfitting, increased complexity and difficulty in model convergence. Variable selection is used to reduce the number of inputs in the database before the modeling process to simplify the models created, to find the most relevant parameters, and to save time and computational resources (Broadhurst et al., 1997). In fact, an optimization algorithm is used in variable selection to select the