Geometry matters: Recent advances, strategies and emerging technologies in engineering carrier particles for lung delivery

Utilizing 3D-printed particles, numeric models and Bayesian optimization to elucidate the influence of carrier geometry in adhesive mixtures

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Abstract

Carrier-based interactive powder mixtures are a cornerstone of drug delivery by inhalation, yet optimization is hampered by the complex interplay of various carrier particle properties including their geometry. Conventional approaches for carrier particle manufacture such as milling, sieving or spray drying can modify multiple attributes simultaneously, making it challenging to assess the effect of particle geometry. To address this, two innovative strategies were applied and are presented in this article: in-silico modeling and the use of 3D-printed carrier particles. Discrete element method simulations allowed the systematic study of virtual drug particle attachment and detachment from carriers of defined geometries. Complementarily, recent advances in two-photon-polymerization enabled the fabrication of millions of uniform, geometry-controlled particles for aerodynamic testing. Four geometries—Sphere, Soccerball, Rollingknot and Pharmacone—were investigated, with the Pharmacone exhibiting superior performance, achieving a fine particle fraction exceeding 16% of the emitted dose, largely attributed to its surface spikes that enhance detachment via chaotic movement and collisions. Building on this, a parametric Satellite geometry was created and optimized through a fully automated in-silico workflow integrating Bayesian optimization, identifying design rules for spike dimensions and surface features. These studies demonstrate that carrier geometry is a critical determinant of drug detachment and aerosolization efficiency. Together, advanced 3D printing and in-silico optimization can provide a powerful framework for designing carrier particles with tailored geometries, offering new opportunities to enhance the performance of dry powder inhalers.

Introduction

In the field of inhaled drug delivery, carrier-based interactive powder mixtures are an established dry powder formulation strategy [1]. The combination of coarse carrier particles with micronized drug can improve powder metering for highly potent active pharmaceutical ingredients (APIs) and have a beneficial influence on aerosolization of the API during inhalation. Carrier-based dry powder inhalers (DPIs) have seen various approaches for product improvement over the last decades [1]. When considering the API, micronization via jet milling is typically used to achieve sufficiently small particles for lung delivery. However, this approach can lead to increased cohesiveness, which in turn reinforces the use of interactive powder mixtures to reduce API-to-API particle interactions. Typically, α-lactose monohydrate is used as carrier particle in interactive blends for inhalation. While a typical lactose crystal resembles a

tomahawk shape [2], the crystals in the final product usually show fragments of the crystal, thus resulting in a variety of particle shapes and sizes.

With controlled crystallization, milling and sieving, narrow particle size distributions within powder batches can be achieved. While dry powder formulations based on lactose carriers are widely used, it remains unknown if more control over the carrier particle properties could lead to better control of the delivered drug. Potentially, this would minimize patient variability and could also improve drug delivery in terms of a higher fine particle fraction (particles aerodynamically smaller than 5 µm). For the carrier particles, which can make up over 97% of the powder blend in some formulations [3], numerous strategies have been researched to improve performance [4]. In order to exercise greater control over the carrier particle and gain more understanding of the impact of individual particle characteristics, it is imperative that the adjustment of the carrier particle can be made in a single parameter without necessitating changes to the entire system. As an example, changing the size of the carrier particle is no challenge itself (e.g., by milling and sieving), but the process of milling would result in different particle geometries, i.e., fragments of the tomahawk, as well as potentially different surface conditions, e.g., the roughness could be increased or a surface amorphization could result in a different surface energy.

One potentially important factor of the particle is the geometry. For engineering the geometry of particles, conventional pharmaceutical techniques are quite limited. For example with spray drying, particles of spherical appearance can be produced [5] as well as collapsed, wrinkled or hollow particles. However, size, roughness and surface energy of the particles will also be affected by the process and will change simultaneously. With more advanced techniques such as controlled crystallization, pollen- or flower-like particles were produced [6, 7]. While the complexity of these particles was higher than that of simple spheres, these techniques still resulted in a distribution of shapes and sizes. In another interesting approach, a molding technique was implemented to produce exact copies of particles, representing the first exactly uniform powder batches [8]. However, compared to the previously mentioned pollen- or flower-shaped particles, these molded particles were rather simple and two-dimensional in their geometry. Limited by the process, at least one surface of the mold was flat and no protruding geometrical features could be used to remove the particle from the mold in one piece. Overall, these approaches are not suitable to identify the impact of a complex 3D carrier particle geometry on the performance of an interactive powder blend.

In this article, we will examine two different, innovative approaches to independently control carrier particle geometry while other parameters are held constant: an in-silico model and carrier particles produced by 3D printing. We will also demonstrate how these models can be used to systematically evaluate and optimize carrier particle geometry.

In-silico model

Carrier particle geometry cannot readily be adjusted independently of other parameters with conventional powder technologies. An in-silico approach allows for particle geometry design with respective 3D-modeling tools combined with the evaluation of these geometries in numerical studies. With numerical simulations based on the discrete element method (DEM), important particle-particle interactions between the coarse carrier and micronized drug particles can be resolved.

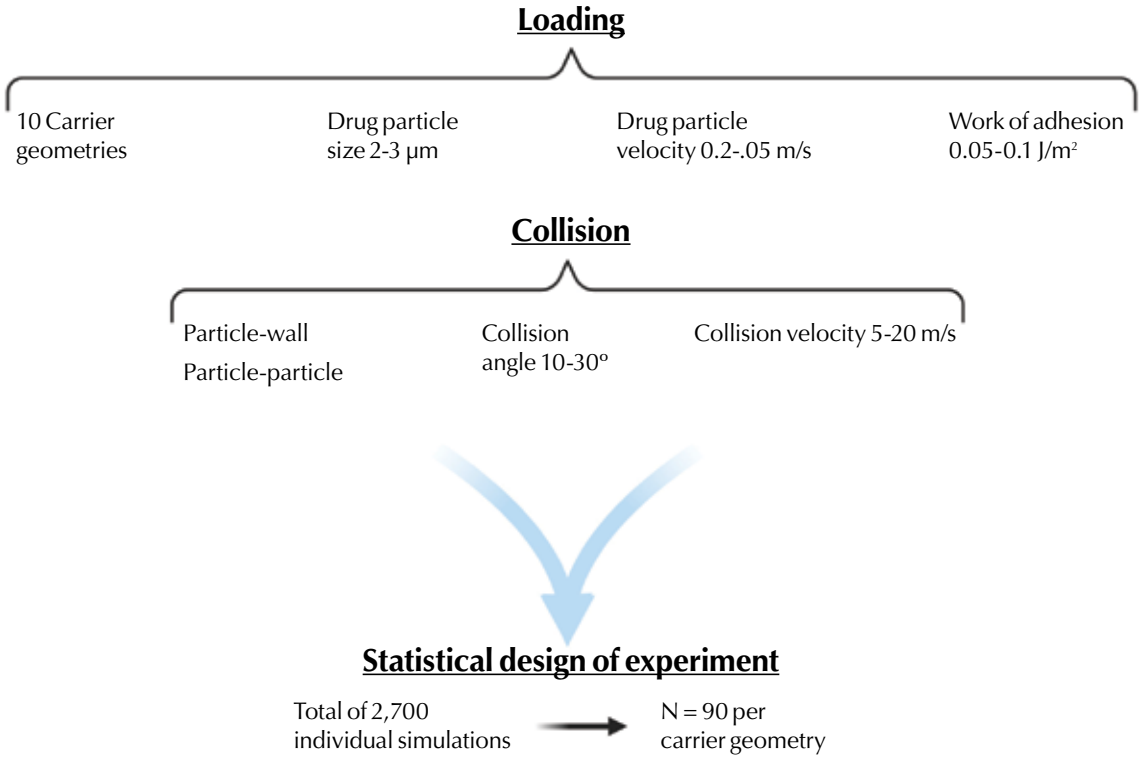
In a recent study, we tested the impact of carrier geometry on the attachment and detachment behavior of fine drug particles (2-3 µm) on a coarse carrier particle with an in-silico model [9]. Three different simulations were used to mimic important steps in the process of the interactive powder mixture from preparation to drug delivery. The interactive powder mixture, represented by a loaded carrier particle, was created first in a loading simulation. A single carrier particle was sprinkled with drug particles, resulting in either attachment or repulsion of the drug particles. The final state of the simulation, a carrier particle randomly loaded with small drug particles representing the interactive powder mixture, was used for detachment analysis. The mechanism of detachment by collision was investigated. Two different types of collisions were tested: 1) two loaded carrier particles colliding at a given angle and velocity and 2) a single carrier particle colliding with a stationary wall. In both, the collision impact led to detachment of the drug in varying amounts. The detachment rate was calculated as the percentage of detached drug compared to the attached drug before the collision and was used as the main indicator for the performance of different carrier geometries. With a Design of Experiments approach, as shown in Figure 1, ten different carrier geometries were tested. Furthermore, to assess whether the influence of carrier geometry was consistent throughout different API particles, the size of the fine particles as well as their material properties regarding the adhesion between drug and carrier were changed. Lastly, conditions for the collision were varied in ranges typical for inhalation.

3D-printed particles

Due to manufacturing limitations, no conventional powder production methods can replicate in-silico modeled particles. However, with advances in additive manufacturing methods, fabrication of such detailed particles is possible via 3D printing. Nevertheless, to make a bulk powder for experimental

Figure 1

Design of Experiments setup for various parameters tested in the in-silico model for both the loading simulation and the collision simulations.



examination, millions of individual particles are needed. Only a very recent advance in printing technology by Kiefer, et al., allowed for the experimental exploration of 3D-printed particles as carrier particles in interactive powder mixtures [10]. The printing method, based on two-photon-polymerization, originally writes a three-dimensional object into a photosensitive resin with a focused laser beam to initiate polymerization and thus creation of the object. With the new development, the printing speed could be increased 49-fold by parallelizing the printing laser focus into a 7 x 7 multi-focus array, making it feasible to print enough particles for our experimental setup. The effect of geometry on aerodynamic performance was investigated for four different particle geometries (see overview in Figure 2 [11]).

Over two million particles were printed for each of the four different geometries, namely the Sphere, Pharmacone, Soccerball and Rollingknot. These particles were used to create interactive blends with micronized budesonide by low shear mixing. The loaded carrier particles are shown in Figure 3.

The powder blends were then tested for aerodynamic performance using a Fast Screening Impactor (Copley Scientific, Nottingham, UK). It was expected that different geometries of the carrier particle would behave differently during the aerosolization process. To minimize aerosolization differences due to the inhaler device, an artificial application device was used, which represents a plain tube with no intrinsic dispersion forces.

Results

The results of both in-silico and 3D-printed approaches for investigating the impact of carrier geometry are shown in Figure 4 [12]. For the in-silico model, only the four geometries that were also tested with printed particles are shown. The average detachment rate derived from both collision simulations serves as an indicator for the fine particle fraction potentially being generated during an inhalation. As described in the literature, the detachment by collision is the driving factor for drug dispersion in the air stream [13]; therefore, a correlation between detachment rate and fine particle fraction is expected. Nevertheless, certain aspects, such as multiple collisions that occur during inhalation and the effect of shear and drag forces for the detachment, are not covered in the simulations.

Different performance was achieved by the different geometries. For the Sphere and the Soccerball, the results were almost identical. The fine particle fraction was about 3-4%, detachment rate by particle-wall collision was about 35% and by particle-particle collision was higher, at about 50%, with no significant differences between the two geometries. The Soccerball geometry represents the Sphere plus the surface indentations that were included to better accumulate the drug particles and shelter them from excess

Figure 2

Workflow of the procession of the 3D-printed carrier particles, from the print, over the mixing with the drug budesonide, to homogeneity testing and aerodynamic assessment of the interactive powder mixture. Reproduced from Wostry, et al. [11] under CC BY 4.0.

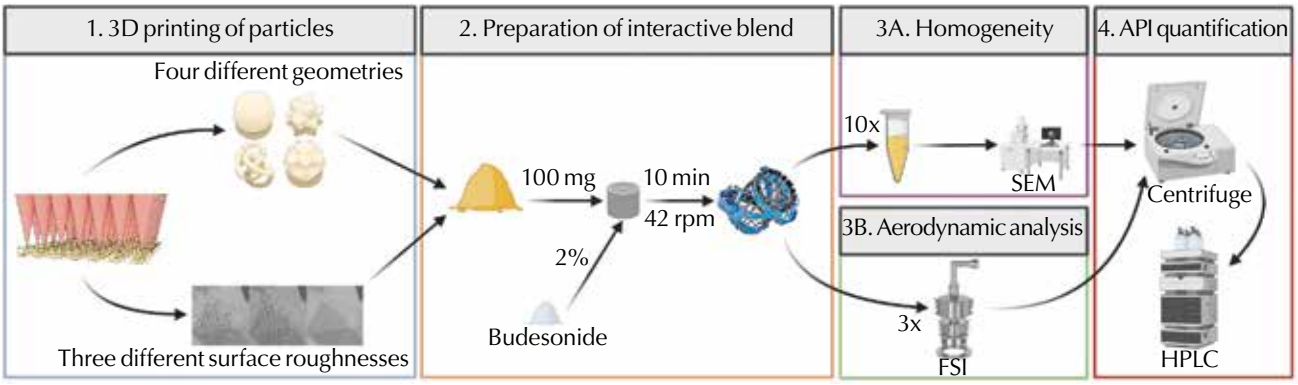


Figure 3

Scanning electron microscope images of the 3D-printed carrier particles in the interactive powder mixture with budesonide in micronized quality as drug; a) Sphere, b) Rollingknot, c) Pharmacone, d) Soccerball. Adapted from Wostry, et al. [11] under CC BY 4.0.

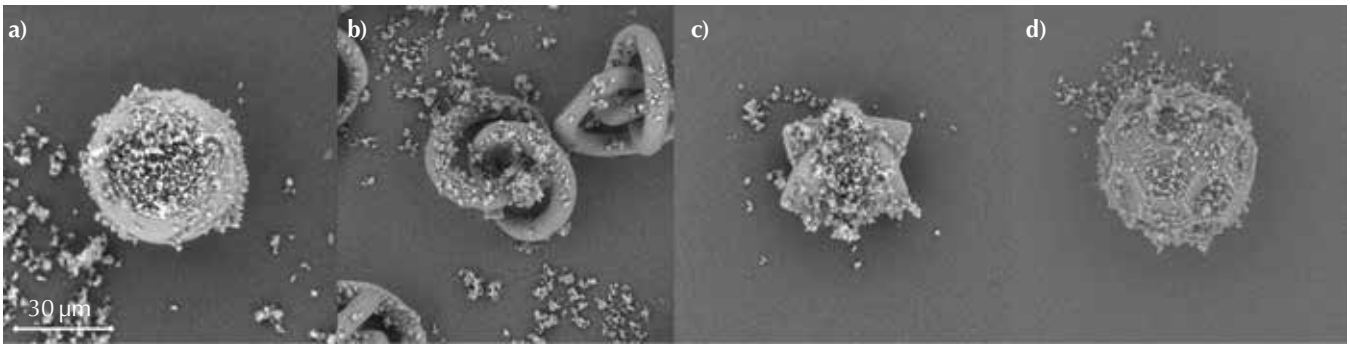
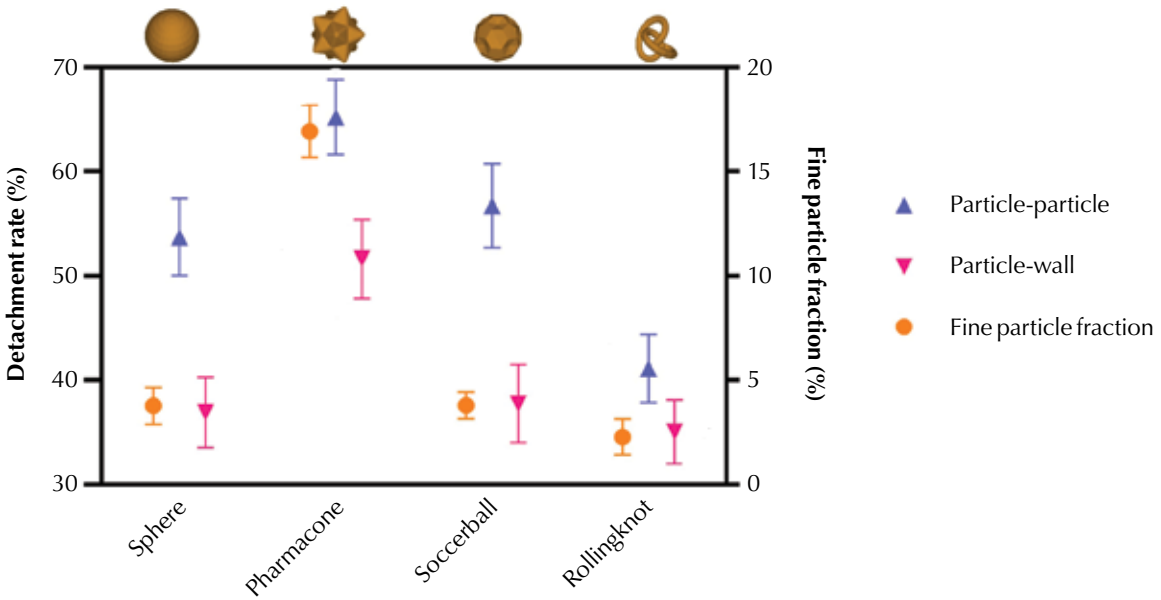


Figure 4

Results of both models for the investigation of different carrier particle geometry, the in-silico model with the detachment rate (left axis) from both collisions, particle-particle and particle-wall, as well as the aerodynamic assessment of 3D-printed particles with the fine particle fraction as the result, error bars = standard deviation, n = 3 for the fine particle fraction and n = 90 for the detachment rate.



press-on forces during mixing and thereby ease their detachment during inhalation. While scanning electron microscopy images (Figure 3) show that drug particles were kept in the indentations, the results did not show an improved fine particle fraction. The Rollingknot did not perform as well in both simulations and experiments. With a fine particle fraction of only around 2%, a particle-wall detachment rate below 35% and particle-particle detachment of only 40%, which were significantly inferior to the other geometries, the Rollingknot showed the worst outcome. One reason could be the particle mass of the Rollingknot. As the detachment of the drug is directly induced by impact forces, those forces correlate with the kinetic energy of the particle in movement and therefore directly with its mass. As the Rollingknot is considerably lighter in weight than the other geometries (14.37 ng per Rollingknot particle vs. 40.10 ng per Pharmacone particle), this could explain its poor performance.

However, one geometry outperformed the other three in all setups: the Pharmacone. With a detachment rate in particle-wall collision of more than 50%, particle-particle collision higher than 60% and importantly a fine particle fraction of about 16%, 4-fold higher than the next best geometry, the Pharmacone clearly outperformed the other particles. The Pharmacone geometry is mainly defined by the spikes protruding from its surface. These spikes seem to be crucial for superior performance. The in-silico models showed that during collision, the spikes lead to a chaotic movement of the particle, thus promoting centrifugal forces, potentially further detaching the drug, as well as increasing the likelihood of additional collisions. This could explain the especially strong performance in the experimental setup with printed particles, where multiple collisions can occur.

The visualization in Figure 4 shows the same trends between simulated detachment rate and experimental fine particle fraction. This supports further implementation of in-silico studies into the research and an investigation of carrier geometry with a performance-guided optimization of the carrier geometry in a quality-by-design approach.

Geometry optimization

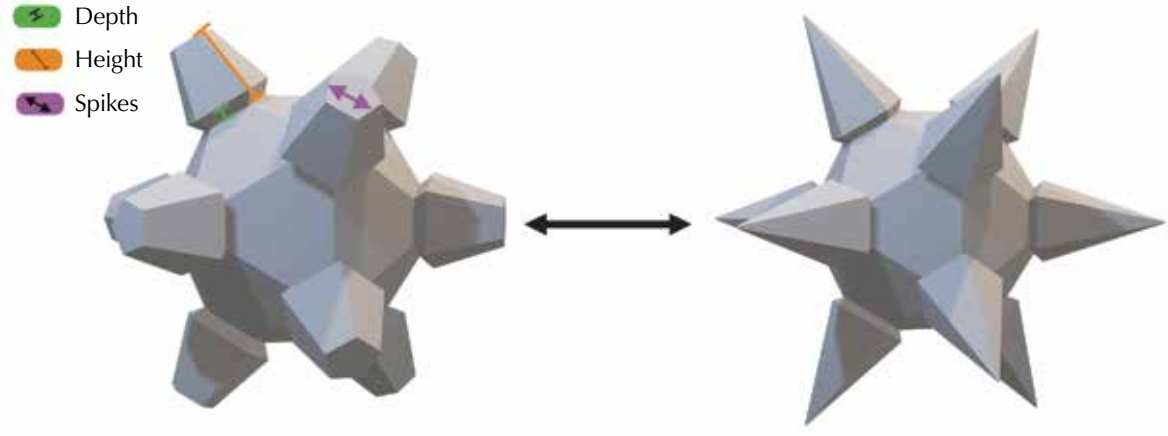
The Pharmacone was found to be the best performing geometry so far, as proven by in-silico studies as well as experimentally with 3D-printed particles. The surface spikes are thought to be an advantage of the Pharmacone. While surface spikes in general are beneficial, the shape of these spikes could also influence the effect on the drug detachment. Therefore, further investigation were made into modification of the carrier geometries to better understand how the geometrical features influence performance and to identify an optimal geometry.

For the geometry optimization in silico, two core aspects were needed: on one side, a modifiable geometry and on the other side, a rational optimization protocol. For the geometry modification, the parametric design software Rhinoceros3D (Robert McNeel & Associates, Seattle, Washington, US) with the feature Grasshopper was used to create a geometry template, the Satellite. It allowed modification of the geometry in three different parameters that defined the surface spikes. The overall height and pointiness of the spikes could be changed, as well as the height of the constriction at the base of the spike, called depth. The geometry template with the adjustable parameters is shown in Figure 5.

For the optimization protocol, an input-output loop was created using the described in-silico studies and Bayesian optimization [14]. As an input, values for the three geometrical parameters were chosen within predefined ranges. Based on the input, the carrier geometry was created and then evaluated in the

Figure 5

Parametric design of the Satellite geometry template, three different adjustable parameters are indicated, on the right the optimized version is depicted.



described in-silico model. As an output, the average detachment rate of both collision simulations, each performed with ten replications, was used. Based on the output data, Bayesian optimization was used to rationally guide the next steps. Bayesian optimization includes the list of input-output combinations already tested and estimates a potential correlation. It then suggests the next input parameters that should be tested for a better understanding of the correlation. This newly created geometry could either be in an area of uncertainty, further exploring the correlation, or could be in an area of highly promising results, thus exploiting the system to find the best geometry. In this manner, iteration-based Bayesian optimization suggests new geometries that are tested in in-silico studies.

The entire process was automated using Python coding for the creation and export of new carrier geometries based on new input data, the setup, calculation and analysis of the in-silico studies for new output data, and the connecting Bayesian optimization, all running in a tight loop over a course of 100 iterations. In total, 2,100 individual simulations were processed without the intervention of the user over a course of two weeks of processing time. The optimization was driven by maximizing the relative detachment. The highest value was found for geometry 87 (Figure 5, right).

The optimization process shows how carrier geometry can theoretically influence drug detachment. The simulation suggests that surface spikes can improve the dispersion and the spikes must be as long as possible, at least in the tested range. Furthermore, pointy spikes showed better results, but a large constriction at the base of the spike did not improve the outcome. The Satellite, in its final form, is not far from the previously tested Pharmacone geometry, which had proven to be superior to the other geometries. Experimental verification will, however, be needed.

Conclusion

The described studies demonstrate the influence of carrier geometry in interactive powder mixtures on drug detachment during inhalation, by testing independently from other parameters defining the carrier particle. Production of homogenous powder blends with adequate flow characteristics is an important aspect in the manufacture of interactive powder blends but was not studied here. The presented methodologies elucidated the impact of geometry and enabled new possibilities for understanding drug detachment crucial for drug delivery to the lungs. The feasibility of producing 3D-printed carrier particles of distinct properties for the creation of realistic, interactive powder mixtures for aerodynamic testing is evident. The development of a fully automated in-silico model can facilitate rapid and extensive screening of diverse potential carrier geometries, in addition to enabling a direct feedback-loop optimization protocol for geometry templates.

While printing speed and choice of printing material are important for a future potential product based on printed particles, further investigations in this direction are promising and the path is open for a next generation of engineered carrier particles.

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