Screening and Optimization of Formulation and Process Parameters for the Manufacture of Inhalable Composite Particles by Spray-drying

Cláudia Moura[1,2], João Vicente[1], Maria Palha[1], Filipe Neves[1], Ana Aguiar-Ricardo[2] & Eunice Costa[1]

[1] Hovione SA, Loures, 2674-506, Portugal

[2] Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Caparica, 2829-516, Portugal

Summary

Drugs for dry powder inhaler systems are conventionally formulated using a carrier-based approach. However, due to blend uniformity issues and poor drug delivery efficiency frequently observed with this formulation strategy, integrated particle engineering and formulation approaches are being explored.

The current work addresses the use of spray drying (SD) to produce composite particles with improved aerodynamic performance (AP), focusing on the screening and optimization of formulation composition and operating conditions. All powders were SD using a BUCHI model B-290. During the screening phase, a Design of Experiments (DoE) was performed using several excipients, sugars and amino acids, previously used in inhalation formulations. Based on particle size and scanning electron microscopy morphology data, yield and AP, the system composed of trehalose and leucine was selected for optimization. The optimization phase consisted on a second DoE to study the influence of SD process parameters on the AP. As in the previous phase, this was assessed by an Andersen cascade impactor using a Plastiape HR model 7 at 60 L/min.

Overall, it was demonstrated that the integrated optimization of composition and process conditions can enable high drug delivery efficiency, with fine particle fraction values of 70% achieved by careful selection of feed concentration, atomization gas flow and solvent system. Most importantly, the results obtained in this work suggest that for low-dosage formulations, development of composite particle systems can be performed independently of the Active Pharmaceutical Ingredient (API), as the incorporation of 1% w/w of API showed negligible impact on the physical attributes and resulting performance of these particles.

Introduction

For many years, the conventional formulation strategy used was the carrier-based approach, where the API previously size-reduced to a mean particle size (PS) of 1 to 5 µm is blended with one or more excipients, usually lactose monohydrate [(1)]. However, this strategy presents several drawbacks such as blend uniformity challenges and poor aerosolization of the API [(1)]. These can only be addressed by optimizing the formulation strategy for each API, which is expensive and time-consuming. To overcome these constrains, several particle engineering technologies were developed to produce carrier-free dry powder inhaler formulations [(1)(2)]. Spray drying (SD) is a particle engineering technology widely used for the manufacture of inhalation powders [(1)(2)(3)]. This technology enables the production of inhalable particles with controlled PS, morphology and density by tuning formulation composition and process parameters such as solvent system, solute concentration, atomization, feed flow rate, drying gas rate, among others. This increased control over the powder properties, allows for the improvement of the powder aerosolization behaviour and dispersibility, which may enable a reduction of the API concentration in the formulation while maintaining the amount delivered to the target site; benefiting the overall safety of the drug product with a reduction in the adverse side effects experienced by patients with respiratory diseases [(3)(4)] . Additionally, from the industry/manufacturer point of view, SD technology represents an easy to operate, flexible, readily scalable and time-effective technology.

In order to take advantage of the SD technology during the preparation of inhalable composite particles, appropriate excipient selection is mandatory. The three sugars and three amino acids (a.a.) were selected following a literature survey on excipients generally regarded as safe and previously used in inhalation formulations. The sugars; lactose monohydrate, trehalose di-hydrate and raffinose penta-hydrate, were selected as glass formers and stabilizers while the a.a.; L-glycine, L-lysine and L-leucine were selected to potentially improve the aerosolization profile. From the selected sugars, only lactose monohydrate is currently approved by regulatory agencies for inhalation, being the most widely used DPI excipient. Regarding the the a.a., L-leucine is receiving more attention in the literature, where it has been reported that its presence enhances the dispersibility and, consequently, the overall aerodynamic performance (AP) of inhalation powders. Its action has been linked to its hydrophobicity, that causes a rapid crystallization/precipitation at the particles surface during the drying process, creating a shell that reduces the inter-particulate forces [(1)].

The main goal of this work was to screen and optimize the formulation composition and SD process parameters in order to improve the drug delivery to the lungs while ensuring process reproducibility and manufacturability.

Experimental methods

The 3 sugars (lactose monohydrate, trehalose di-hydrate and raffinose pentahydrate) and 3 a.a. (L-glycine, L-lysine and L-leucine) were all considered as viable candidates during an initial screening phase. A BUCHI model B-290 was used to conduct a resolution III half-factorial design (2^{3-1}) by varying the sugar (C_sug.) and a.a. concentration (C_a.a.) in the feed and SD outlet temperature (T_out) – **Figure 1**. All remaining parameters were kept constant with the following values: solution feed flow (F_feed) at 7 g/min, atomization gas flow (Atom) at 30 mm in the rotameter and drying gas flow (F_drying) at ~35±5 kg/h.

The 36 powders generated (3 sugars X 3 a.a. X 2^{3-1} design) were characterized by scanning electron microscopy (SEM), differential scanning calorimetry, X-ray powder diffraction (XRPD) and Karl-Fischer. The emitted mass (EM) was determined by a dose uniformity sampling apparatus (DUSA) with 20 mg of formulation filled in HPMC size 3 capsules using a Plastiape HR model 7 at 60 L/min for a pressure drop of 4 kPa. Based on the process yield and on the EM, 4 systems were selected for further investigation: raffinose:leucine, raffinose:lysine, trehalose:leucine and trehalose:lysine.

The previous four systems were tested as 100% excipient composite system and with 1% w/w of the total solids (Tsolid) replaced by iopamidol, to assess the influence of a low dose of active compound in the powder performance. However, for the sake of space limitation, only the trehalose:leucine system data will be presented (**Figure 1**). This system is composed of 2.5% w/w of total solids in an aqueous feed, with a 4:1 ratio of trehalose:leucine and the outlet temperature selected was 95 ºC. The AP was assessed on an 8 stage gravimetric Andersen cascade impactor (ACI8) with 20 mg of formulation filled in HPMC size 3 capsules using a Plastiape HR model 7 at 60 L/min for a pressure drop of 4 kPa.

The trehalose:leucine system (100% excipient) was further optimized using a 2^3 full factorial design (8 experiments + 2 centre points + 1 centre point replicate). The three varied parameters were C_feed, Atom and percentage of ethanol (%Et) in the water:ethanol solvent system (**Figure 2**). All remaining parameters were kept constant with the following values: F_feed at 7 g/min, T_out at 95 ºC, "sugar:a.a" ratio at 4:1, F_drying at ~35±5 kg/h. SEM micrographs were obtained for all powders and the AP was assessed as previously described. The FPF (< 4.7 µm) was expressed as a percentage of the total mass emitted from the capsule.

A statistical analysis to quantify the impact of the input parameters (C_feed, Atom and %Et) on the output (FPF%) was performed using MODDE 9 software from UMetrics (**Figure 3**).

Results and Discussion:

The screening phase allowed a progressive elimination of several systems based on the analytical characterization (e.g. solid state results) of the resulting powders (data not shown). By ranking the process yields (Y) and the DUSA results, only 4 systems fulfilled the target requirements (Y > 90% and EM > 90%): the combinations involving trehalose, raffinose, lysine and leucine.

According to the XRPD results, 2 out of the 4 powders were in the amorphous form, with the 2 formulations containing leucine showing crystalline peaks (data not shown). Only the AP of one system (2.5% TSolids, with a trehalose:leucine ratio of 4:1, dried with a T_out = 95 ºC) is shown in **Figure 1**, where it could be observed that the FPF of the composite particles as is and with the addition of 1% of total solids of iopamidol resulted in a FPF of 16.1% and 15.5% respectively. Based on the ACI8 results from all 4 systems (data shown for the trehalose:leucine system only – **Figure 1**), the addition of 1% of iopamidol to the formulation did not have a significant impact on the performance given a similar FPF of the total emitted mass from the capsule, FPF_{TM}(%); although the systems containing leucine presented an increased FPF (data not shown). This may be an indication that the development process of these composite powders may be carried out independently of the API, provided that its concentration is kept at low values. Regarding the improved FPF of systems containing leucine, the most likely explanation is that, with the appropriate SD conditions, the leucine molecules tend to precipitate/crystallize on the particle surface, normalizing the dispersibility of the particles, while the trehalose and the API remain inside as an amorphous glass. Further analytical characterization will be required to test the hypothesis.

As a result of the knowledge gained during the screening process, an optimization phase was carried out for the trehalose:leucine system varying 3 process parameters in the SD step: C_feed, Atom and %Et between [0.5 – 3.5]%, [40 – 60]mm and [0 – 20]%, respectively. The factorial design and the aerodynamic performance results is presented in **Figure 2**.

As shown by *in vitro* impaction measurements, it was possible to optimize the SD conditions in order to increase the FPF_{TM}(%) values from 16 up to 70%. It was also observed that the higher the Atom and the %Et combined with the lowest the C_feed, lead to greater FPF. As shown on the SEM micrographs (**Figure 2**), these 3 parameters control

the PS and morphology. The particles shown in the SEM micrograph of W1 and WE1 were very similar, although WE1 seems to present higher number of smaller particles and even some fragments of broken particles likely due to the presence of ethanol. The SEM micrographs of W5 and WE3 represent the powders with the lowest and the highest FPF, 19 and 70% respectively, which correspond to the particles with larger and smaller PS.

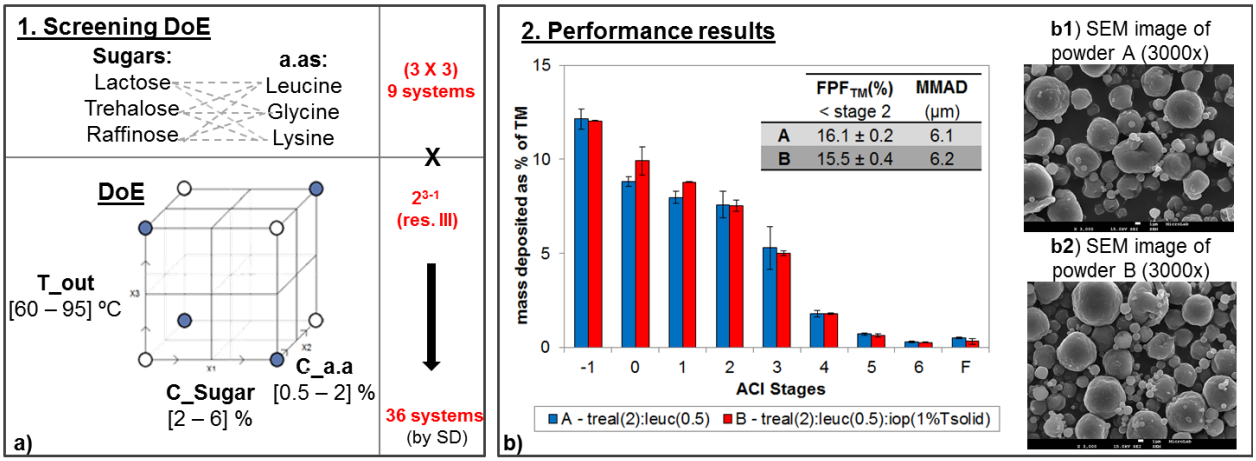

Figure 1 – Screening phase: a) design structure and ranges explored; b) aerodynamic performance and SEM micrographs for two of the powders.

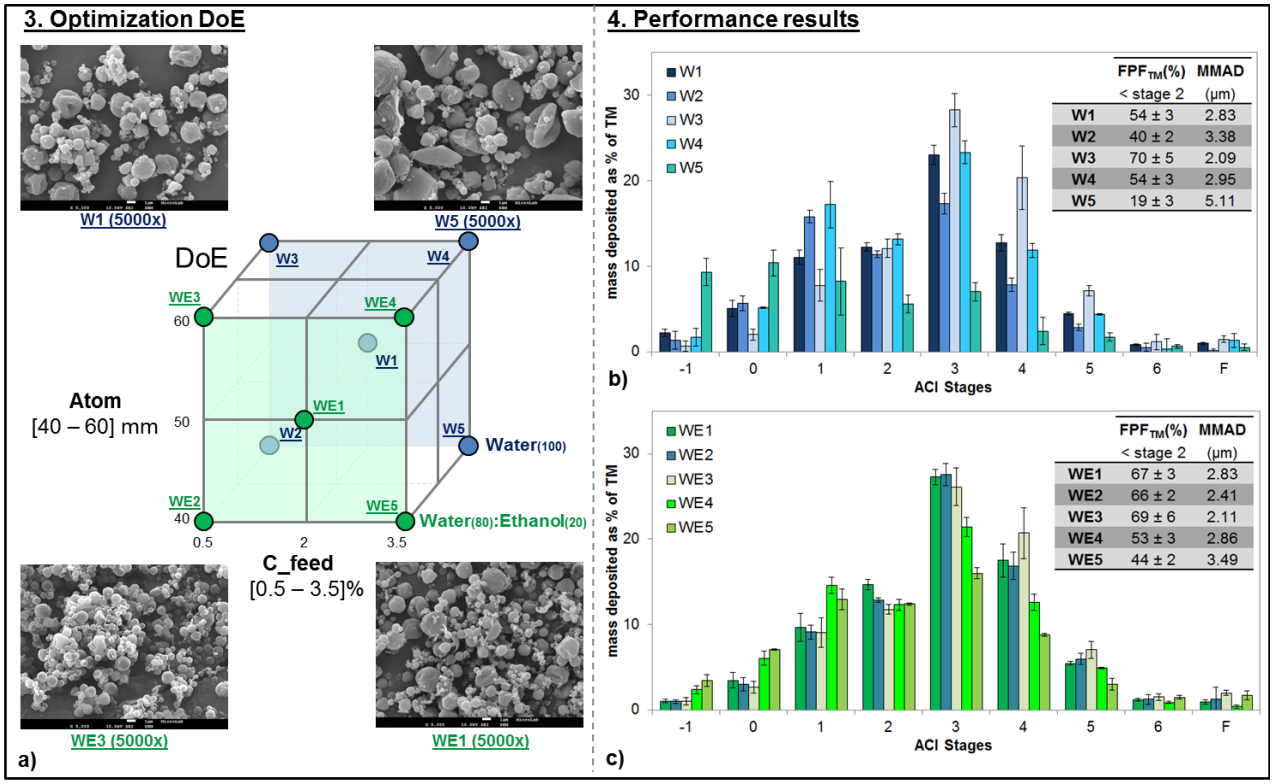

Figure 2 - a) Optimization phase: a) design structure and ranges explored for the trehalose:leucine system, together with SEM figures of some runs; b) AP of water-based systems; c) AP of water:ethanol systems.

Although the manipulation of SD process parameters allowed to reach FPFs as high as 70%, it is important to ensure the economic viability of the process; a C_feed of 0.5% would not translate to a commercially viable scenario, as the very low solids throughput would be a very expensive SD process from a price/kg perspective.

For this reason, a statistical analysis was carried-out in order to quantify the impact of C_feed, Atom and %Et (inputs) in the FPF (output). The derived partial least squares (PLS) regression model (**Figure 3**) shows a very good fit (R^2) and predictability (Q^2), meaning that this model can be used for future optimization of trade-offs between process throughput and aerodynamic performance, that will always need to be conducted on a product-by-product basis.

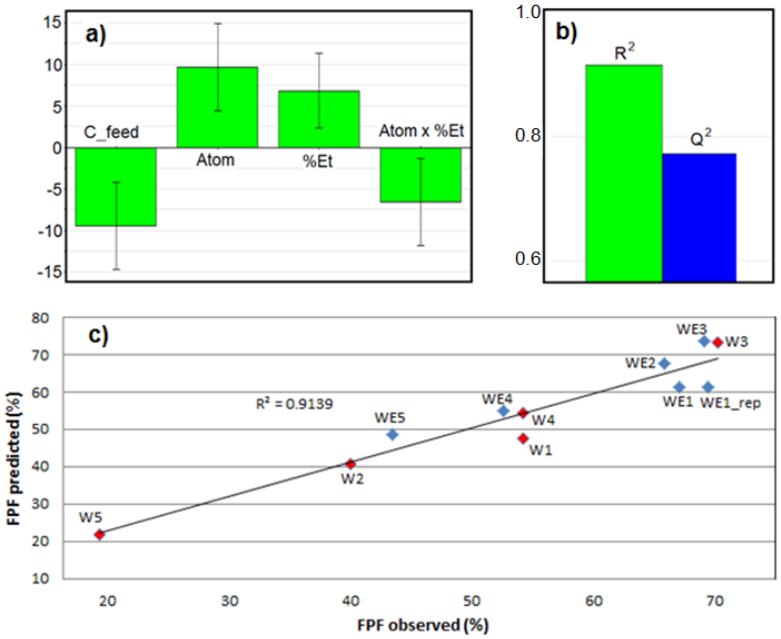

Figure 3 - Statistical analysis: a) model coefficients (scaled & centered); b) model fit data; c) Observed vs Predicted plot.

Conclusions:

The integrated optimization of spray dried composite particles for inhalation from a composition and a process parameters perspective have shown that the development can potentially be performed without the incorporation of an API since the addition of a model drug at low concentrations did not have a significant impact on the powder properties nor aerodynamic performance. More importantly, this might be an indication that an API-independent profile may be obtained for these systems as long as the target dose is low. In addition, this study has shown that the aerodynamic deposition profile can be fine-tuned to obtain FPF ranging from 16 up to 70% by increasing the Atom and %Et and decreasing the C_feed, following well-behaved prediction models.

References:

1. Healy AM, Amaro MI, Paluch KJ, Tajber L: Dry powders for oral inhalation free of lactose carrier particles. Adv Drug Deliver Rev. 2014;75:32-52.
2. Hoppentocht M, Hagedoorn P, Frijlink HW, Boer H: Technological and practical challenges of dry powder inhalers and formulations. Adv Drug Deliver Rev. 2014;75:18-31.
3. Xu EY, Guo J, Xu Y, Li HY, Seville PC: Influence of excipients on spray-dried powders for inhalation. Powder Technol. 2014; 256:217–223.
4. Nandiyanto ABD, Okuyama K: Progress in developing spray-drying methods for the production of controlled morphology particles: From the nanometer to submicrometer size ranges. Adv Powder Technol. 2011;22(1):1–19.