

A Design of Experiments approach to optimising spray drying yield and production efficiency of a model inhaled powder for global health applications

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Summary

Pharmaceutical products developed for low-income markets may face greater challenges in covering manufacturing costs while meeting affordable costs of goods in these settings. Inhaled products for these markets must address the cost of manufacture and how this impacts the affordability of the product to the end-user in order to improve chances of long-term sustainable healthcare outcomes. In this example of an inhaled powder product designed for use in low-income markets, addressing the cost of manufacture require optimisation of the raw yield and speed of production spray drying process by increasing process parameters such as the concentration of feed solution and feed solution pumping speed. However, increasing powder production in this way may influence the carefully engineered powder particle characteristics which in turn will affect dose delivery. To address this issue, the complex nature of the relationships between spray drying processing parameters and physical powder attributes critical to product performance were characterised using a Design of Experiments (DoE) approach. Response Surface Methodology (RSM) was then employed to construct a predictive model and carefully optimise the processing parameters for maximal powder yield and spray drying efficiency while maintaining tight limits on particle size, moisture content, and glass transition temperature.

Key message

A DoE (2⁴-CCD) approach was used to increase spray drying yield and powder production efficiency while maintaining critical quality attributes of trehalose powder particle for deep lung penetration, in order to better address inhaled product affordability challenges experienced by low-income countries.

Introduction

Maternal mortality is one of the most inequitable statistics in global health due to an estimated 300,000 woman dying of complications relating to childbirth and pregnancy, with up to 99% of these deaths occurring in low and lower-middle income countries (LMICs) [1]. Postpartum haemorrhage (PPH) is one of the most common causes of maternal death and disproportionately affects mothers in low-income countries due, in part to inadequate access to medicines. Oxytocin injection (IV/IM) is an effective therapy for prevention and treatment of PPH and is included in the World Health Organisations list of essential medicines as the gold standard of care. While oxytocin injection is the standard of care for PPH, barriers to access exist in LMICs around its heat-sensitivity and the need to be refrigerated during storage. Consequently, the quality of oxytocin ampoules at the point of use in sub-Saharan Africa varies considerably [2]. The inhaled oxytocin project seeks to develop a heat-stable, spray dried oxytocin product for pulmonary delivery, a reformulation that has the potential to improve PPH outcomes by offering a more sustainable alternative to traditional IV and IM methods. However, an ampoule of injectable oxytocin in LMICs is priced at approximately \$0.33 USD [3] and therefore, the long-term viability of innovations like inhaled oxytocin are acutely challenged by the willingness and ability of product financiers to supply and manufacture spray dried powders at a comparable cost to the end-user. For an inhaled oxytocin product, it is imperative that manufacturing is as cost-effective as possible in order to align with sustainability goals and provide the most affordable final product to users in low-resource settings.

Spray drying has become an increasingly popular manufacturing method of inhalable pharmaceutical powders, particularly those containing proteins and peptides, due to the heat stability offered when spray drying parameters are tightly controlled [4, 5]. There are many products, both marketed and in development [6] that utilise spray drying technology however, to the author's knowledge there is no commercially available product for pulmonary delivery and systemic uptake, that is completely spray dried. Spray drying trehalose and oxytocin has had proven potential in pre-clinical and early clinical studies [7, 8] however, a commercial scale manufacturing process is required that addresses the affordability challenges of a product for low-resource settings. However, spray drying a potent hormone like oxytocin requires substantial containment from an R&D scale to commercial manufacture. In order to address this challenge, oxytocin was removed and replaced with trehalose during development in accordance with internal studies that indicate similar physical characteristics of the placebo particle and

the active particle. Further, reports discussing the benefits of optimising spray drying yield have emerged due to the variable nature of yields observed when using standard bench-top systems and, the expenses of low yield processes even at an R&D scale [9]. Spraying drying yield is often related to powder adhesion to the inner surfaces of the cyclone and poor collection efficiencies of lab scale systems, which in turn can be influenced primarily by the inlet air temperature and liquid feed rate into the spray dryer [10]. In order to improve yield and powder production efficiency while maintaining critical quality attributes of particles for inhalation, the present study uses a pilot scale spray dryer and a DoE approach to investigate the influence liquid feed rate, inlet-air temperature, atomising gas feed rate and feed solution concentration on production efficiency metrics (yield and spray drying throughput) of trehalose powders.

Materials

Milli-Q® water (Merck-Millipore, Darmstadt, Germany), D-(+)-Trehalose dihydrate (Sigma-Aldrich, Castle Hill, Australia), L-leucine (Sigma-Aldrich, Castle Hill, Australia).

Methods

Spray drying

All batches (n=30) were spray dried using a ProCept 4M8-TriX spray dryer (ProCept, Zelzate, Belgium) with a 0.4 mm bi-fluid atomising nozzle using air as the drying and atomising gas (feed rate, 500 L/min). Process parameters ranges were as follows; atomising gas feed rate from 11 to 19 L/hour, inlet air temperature from 140 to 200° C, feed solution flow rate from 1 to 7 g/min and, feed solution solid concentration from 3 to 11% w/w. Powder collected from the spray dryer was immediately sealed and weighed on an analytical balance.

Particle size distribution

Determined by laser diffraction by Malvern Mastersizer 2000 (Malvern Instruments, Worcestershire, UK) with a Scirocco 2000 dry dispersion unit using 2 bar of air pressure for optimal powder dispersion and powder deagglomeration. Powder samples were analysed in triplicate (n=3).

Moisture content

Determined by coulometric Karl-Fischer titration using an 874 USB Oven Sample Processor (Metrohm AG, Herisau, Switzerland). Samples were weighed under low humidity (< 30% RH), analysed in triplicate (n=3) and heated to 150° C by the oven unit with a 50 L/min dry nitrogen as the carrier gas. Data was analysed using Tiamo 2.5 software (Merck-Millipore, Darmstadt, Germany).

Glass transition temperature

Measurements made with a Perkin-Elmer DSC 8500 (Perkin-Elmer, MA, USA) differential scanning calorimeter. Powder samples were weighed into 50 µL aluminium DSC pans and crimped under low humidity (< 30% RH). Thermal data was collected in heating mode, with a dry nitrogen gas at a flow rate of 20 L/min to purge cell, temperature gradient 10° C/min ramp from -10 to 170° C.

Design of experiments (2⁴-CCD)

All factorial design analysis and response surface plotting was conducted using Design Expert® software V.12 (Stat-Ease Inc., MN, USA). A randomised, non-blocked, 2⁴ (2 level, 4 factor) factorial central composite design (CCD) (n=24) was chosen to investigate the 4 chosen spray drying process parameters and allow fitting of second order response surface models to the data obtained. Centre points (n=6) were chosen in order to calculate the experimental error and improve precision when fitting models. The 2⁴ CCD was augmented with 8 axial points ($\alpha = -2$) to make the design compatible with more complicated second order RSM designs. A desirability function was used to find the optimal process parameter levels and incorporated limits for the d(10), d(50), d(90), span, moisture content, glass transition temperature, yield and production efficiency. Statistical analysis of variance (ANOVA) used to determine the significance (p-value) of the main factors as well as their relevant interactions. Significant parameters were included in the final model.

Results & Discussion

Design of experiments (DoE) is a well-established methodology for identifying and optimising process parameters while maintaining certain product specifications. Many studies have successfully optimised spray drying processes for pharmaceutical powder production, whether the focus be on particle size, morphology, biological activity or crystallinity of excipients [4, 9-11]. More recently, DoE approaches have successfully been applied to the production of inhalable powders [12-15]. Figure 1 visualises the change in each response when increasing or decreasing coded processing parameter levels (-1 to 1), within the mapped experimental space. When increasing the liquid feed rate and feed solution concentration an increase in yield (**A**), production efficiency (**B**), particle size (**C**) and moisture content (**D**) was observed, with only the glass transition temperature (**E**) decreasing. Spray drying literature primarily points to reductions in yield as resulting from loss of powder fines through impaired cyclone

collection efficiency or powder deposition and build-up on the inside of the spray dryer. It has been previously established that increasing the liquid feed rate increases the volume of the solution being dispersed by the nozzle per unit time and thus increases the droplet size, and eventual particle size [11, 16]. Similarly, higher concentrations of solids in the feed solution will generally produce larger particles that have a greater likelihood of being retained in the collection vessel [12]. This study agrees with previously reported findings that feed solution or ‘solids’ concentration had a significant effect on yield [15, 16]. Conversely, increasing the atomising gas feed rate decreased these same responses. By reducing the droplet size, the drying rate of the droplet is changed, impacting the particle size and the moisture content [12].

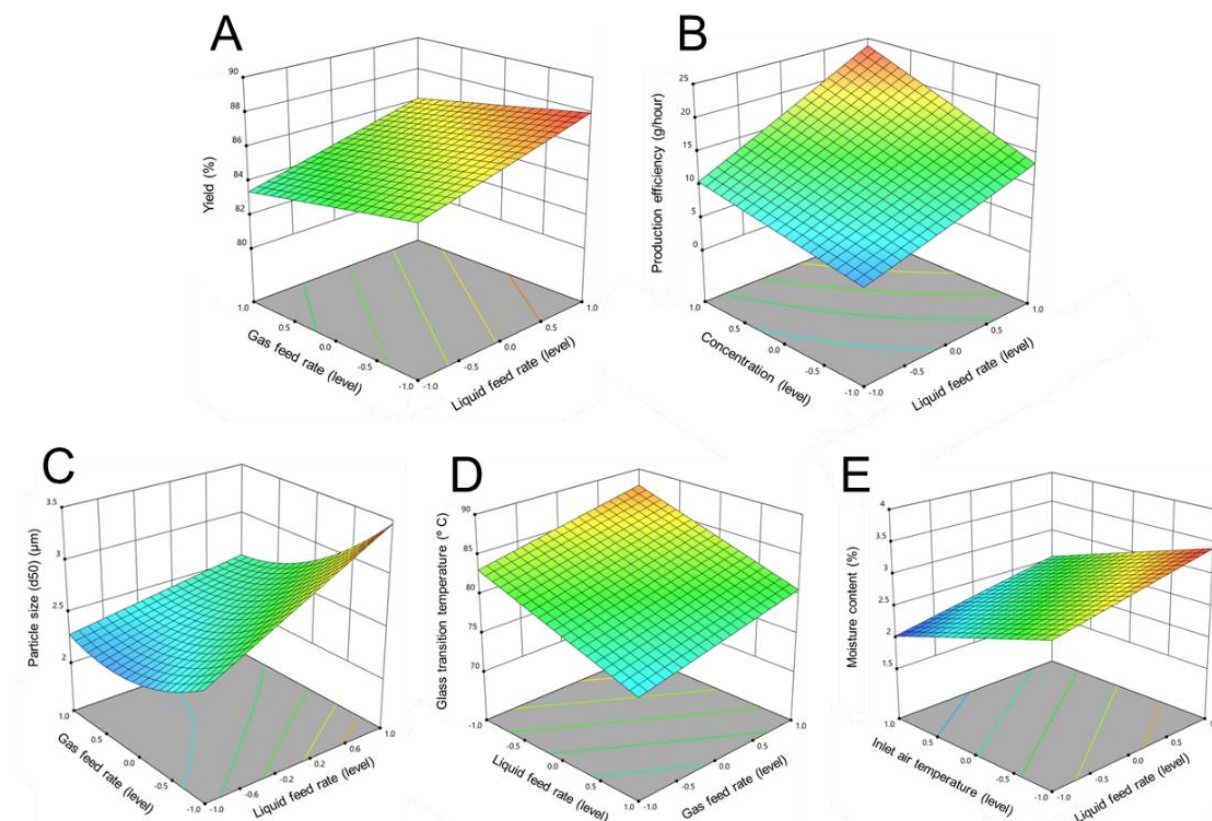


Figure 1: Surface plots of; yield (A), production efficiency (B), particle size (d50) (C), glass transition temperature (D) and moisture content (E) as a function of the two processing parameters that induce the largest change in each respective

The models in Figure 1 were predominately non-linear with the exception of glass transition temperature and moisture content. This agrees with current literature showing gas feed rate to have non-linear relationships with particle size, yield and moisture content for similar formulations [4, 13].

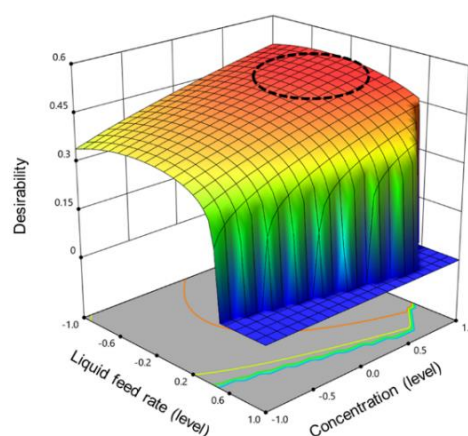


Figure 2: Surface plot of desirability model (0-1) as a function of liquid flow rate and concentration levels (-1 to +1), temperature (+1) and gas feed rate (0) were held at constant. Highest desirability and region of best yield (circled).

All four of the chosen spray drying processing parameters had significant effects on yield and production efficiency, with concentration and liquid flow rate providing the largest increases in yield of all the interactions. From these response-process parameter relationships a desirability (Figure 2) model was

generated to provide maximal yield and production efficiency while maintaining powder particle characteristics. Processing parameters that provided the optimal desirability (Figure 2, red region) produced powders that were consistent across all measured responses, were within the 95% confidence interval for each response and were within the particle requirements for deep lung penetration (Table 1). The raw yield and production efficiency were improved by 12.4 % and 8.6 g/hr respectively, when compared to the reference spray drying conditions. The reference product maintained a higher glass transition temperature (87.7° C) than the reference product (81.1° C).

Table 1: Summary of the spray dried model validation samples

Process parameter	Yield (%)	Production efficiency (g/hr)	Moisture content (%)	Glass transition temperature (° C)	Particle size (d50) (µm)
Reference*	73.0	6.0	2.40	87.7	2.3
Model limits†	83.4 - 86.4	14.5 - 14.9	1.6 - 2.7	79.4 - 94.6	2.3 - 2.8
Validation run‡	85.4	14.6	2.00	81.1	2.3

*Reference product values from previous optimisation studies. †Expected limits defined by the 95% confidence interval for each response. ‡ Mean (n=3)

Conclusions

The reality of spray dried powder production is that material, labour and manufacturing costs, all contribute to the final product price and affordability to the end users. While spray drying is already an efficient and economical production method, minimising the time spent using large-scale spray dryers will be a key determinant of meeting product affordability, in line with sustainability goals for an LMIC orientated product. There are many DoE studies on powder production for global health applications however, it is uncommon for reports to incorporate the benefits of speed of manufacture into predictive models. This study expanded on previous work [14] by using RSM and a full 2⁴ factorial CCD in order to investigate the influence of spray drying process parameters on the yield and efficiency of the spray drying process and to provide an optimal set of parameters for maximising yield and minimising time spent during manufacture, while maintaining critical powder particle quality attributes. The resulting model was predictive and provided empirical improvements to powder yield and production efficiency while maintaining critical quality attributes of a powder particle for deep lung penetration. These results are encouraging for the potential future applications of spray drying as the commercial production method of cost-constrained pharmaceutical products for global health applications.

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