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Poster Number 15M0330

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2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER
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PURPOSE

Introduction

Liquid vaccines need to be stored at 2-8 °C. Dependency on **cold chain** makes distribution of liquid vaccines complex and expensive that could potentially be overcome by using dried **powder vaccines**. **Spray drying (SD)** is an established method for drying pharmaceutical biologicals. Drying liquid vaccines by SD method can produce powders with desired physiochemical and morphological properties (fig 1).

The issue

Spray drying process for experimental vaccines are mostly optimized by **one-factor-at-a-time (OFAT approach)**, that has several disadvantages (fig 2). In contrast to OFAT, **Design of Experiments (DoE)** is a structured approach to identify critical and non-critical parameters for production and this approach can be applied to produce dry powder vaccines.

The goal

Therefore, the objective of this study was to investigate the use of a Design of experiment (DoE) approach to systematically screen and optimize the spray drying process variables and predicting product quality parameters for dried powder vaccine.

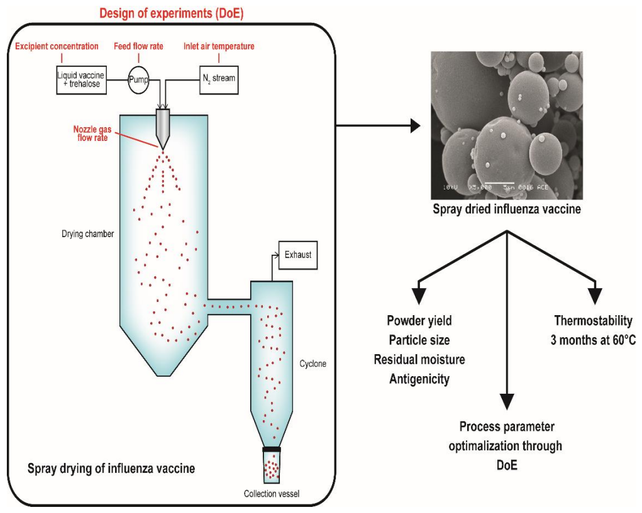

Figure 1: Spray dried influenza vaccine

METHOD

Whole inactivated influenza virus (WIV) vaccine was used as the model vaccine with Trehalose (100-150 mg/mL) as stabilizing excipient. The process parameters investigated were **inlet air temperature** (110-160 °C)**, nozzle gas flow rate** (7.3-17.5 L/min) and **feed flow rate** (1.0,3.4 and 4.5 mL/min)**.** The WIV vaccine powder (product parameters) investigated were **particle size**, **residual moisture content**, **powder yield** and **Antigenicity**. Spray drying experiments were performed based on the **Central Composite Family (CCF) design** consisting of **23 experimental runs**. Results obtained from vaccine powder analysis were analyzed with software **MODDE 10.0** and the relation between different parameters was studied.

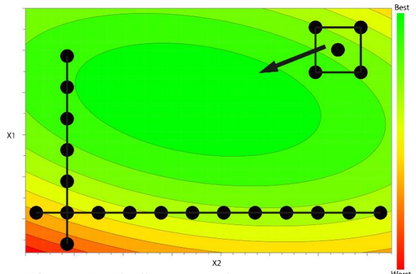

Figure 2: Finding an optimum

One Factor At a Time
- one factor at a time
- no interaction b/w factors
- more experiments

Design of Experiment:
- direction of optimum
- interaction b/w factors
- maximum Information with minimum experiments

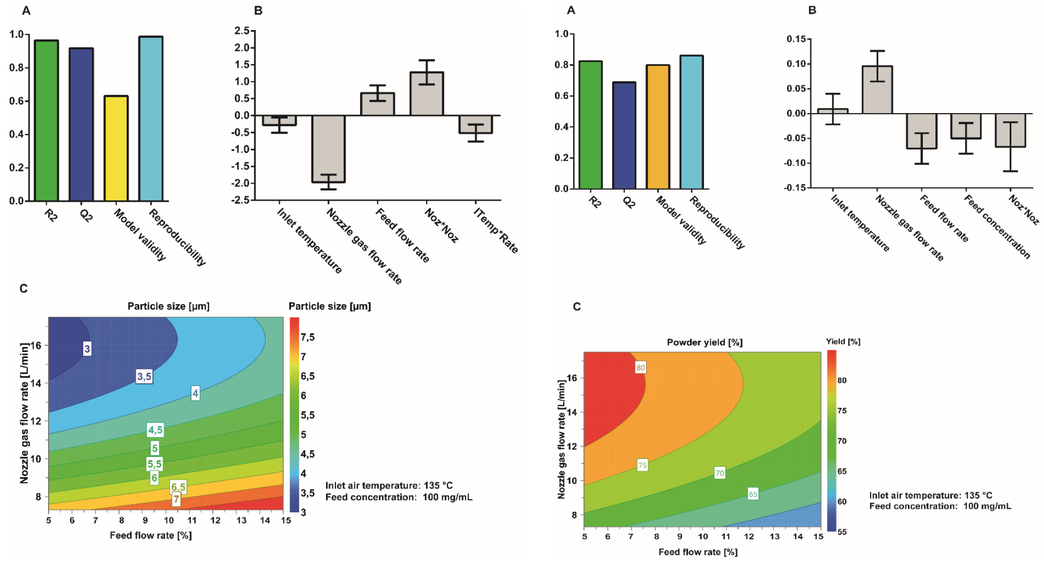

Figure 3: Regression model Particle size

Figure 4: Regression model Powder yield

A: Summary of fit plot for particle size. R2 (Goodness of fit, 1 = perfect model). Q2 (Goodness of prediction, values greater than 0.5 is a good fit). Model validity (value greater than 0.25 indicates good fit). Reproducibility (greater than 0.5 indicates a small experimental error) B: Regression coefficients for particle size/ powder yield. C. Response contour plots for particle size(left) / powder yield(right). The effect of the two most influential factors (as observed from Fig B) was taken into account and other factors were kept constant. The color regions represent the predicted response for defined parameter settings.

Published: Kanojia *et.al*, International journal of pharmaceutics. 2016;511(2):1098-111. doi: 0.1016/j.ijpharm. 2016.08.022. PubMed PMID: 27523619.

RESULTS

Vaccine powders with a broad range of **physical characteristics** (RMC 1.2- 4.9 %, particle size 2.4 -8.5 µm and powder yield 42-82 %) were obtained. WIV showed **no** significant **loss** in **antigenicity.**

Furthermore, descriptive models (fig 3 and 4) generated by DoE could be used to predict process settings (inlet air temperature, nozzle gas flow rate, feed flow rate and excipient concentration), that subsequently could be used (set) to generate a dried WIV powder with predefined (predicted) characteristics (fig 5). Moreover, the spray dried vaccine powders retained their **antigenic stability** even after **storage for 3 months at 60 °C**.

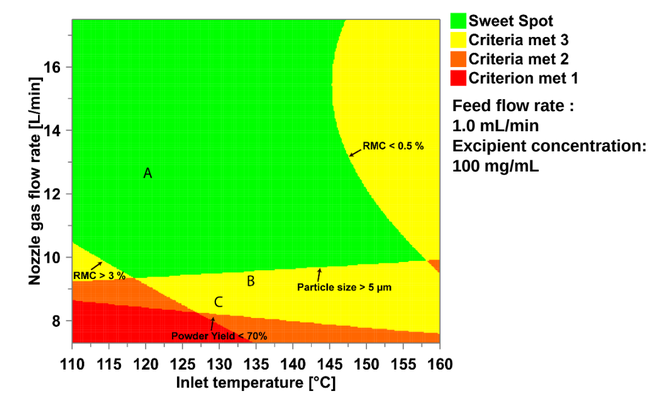

Figure 5: Predicted Design Space. A,B and C are spray drying experiments performed to confirm the prediction abilities of the model.

Target profile criteria:

Particle size:1-5 µm
Residual Moisture Content: 1-3 %
Powder Yield: >70 %
Outlet temperature : below 100 °C

CONCLUSION

The current study successfully demonstrates the application of QbD principles and the DoE approach in the development of a dry powder influenza vaccine formulation. The WIV vaccine powder was thermostable that could be potentially used for pulmonary administration.

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