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A Design of Experiment approach to predict product and process parameters for a spray dried influenza vaccine

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ABSTRACT

Spray dried vaccine formulations might be an alternative to traditional lyophilized vaccines. Compared to lyophilization, spray drying is a fast and cheap process extensively used for drying biologicals. The current study provides an approach that utilizes Design of Experiments for spray drying process to stabilize whole inactivated influenza virus (WIV) vaccine. The approach included systematically screening and optimizing the spray drying process variables, determining the desired process parameters and predicting product quality parameters. The process parameters inlet air temperature, nozzle gas flow rate and feed flow rate and their effect on WIV vaccine powder characteristics such as particle size, residual moisture content (RMC) and powder yield were investigated. 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 as revealed by hemagglutination test. Furthermore, descriptive models generated by DoE software could be used to determine and select (set) spray drying process parameter. This was used to generate a dried WIV powder with predefined (predicted) characteristics. Moreover, the spray dried vaccine powders retained their antigenic stability even after storage for 3 months at 60 °C. The approach used here enabled the generation of a thermostable, antigenic WIV vaccine powder with desired physical characteristics that could be potentially used for pulmonary administration.

1. Introduction

Many existing vaccines are currently distributed and administered in a liquid form. Liquid vaccines need to be stored at 2–8 °C to remain stable. This dependency on a steady cold chain makes vaccine distribution complex and expensive, especially in developing countries (Wang, 1999). Dried vaccines can overcome this requirement for a cold chain, as they possess a longer shelf life at elevated temperatures (Geeraedts et al., 2010; Smith et al., 2015). Moreover, dry powder vaccine formulations have the potential to be used for alternative vaccine delivery routes, such as the intranasal, pulmonary or oral routes (Dicko et al., 2000; Giudice and Campbell, 2006; Tonnis et al., 2012; Amorij et al., 2010).

An established method to produce dried biologics is spray drying. Spray drying has the advantage over traditional drying techniques (such as freeze-drying) that it is relatively fast and has lower operating costs. Moreover, it results in a dispersible fine powder compared to a dry cake as obtained by freeze-drying, which may enable further powder handling and usage for alternative delivery routes.

Powders with different physiochemical and morphological properties can be obtained by spray drying. The powder properties depend on the applied process parameters and composition of the liquid feed (Crowe et al., 1994; Jain and Roy, 2008). The spray drying process consists of nebulization of a liquid product, generating aerosols, into a heated gaseous drying medium, resulting in a dry powder (Fig. 1). The large surface area of the aerosols results in a relative rapid drying process. Depending on

Abbreviations: QbD, quality by design; DoE, Design of Experiments; QTTP, quality target product profile; WIV, whole inactivated influenza virus; XRD, X-ray diffractometry; DSC, differential scanning calorimetry; RMC, residual moisture content.

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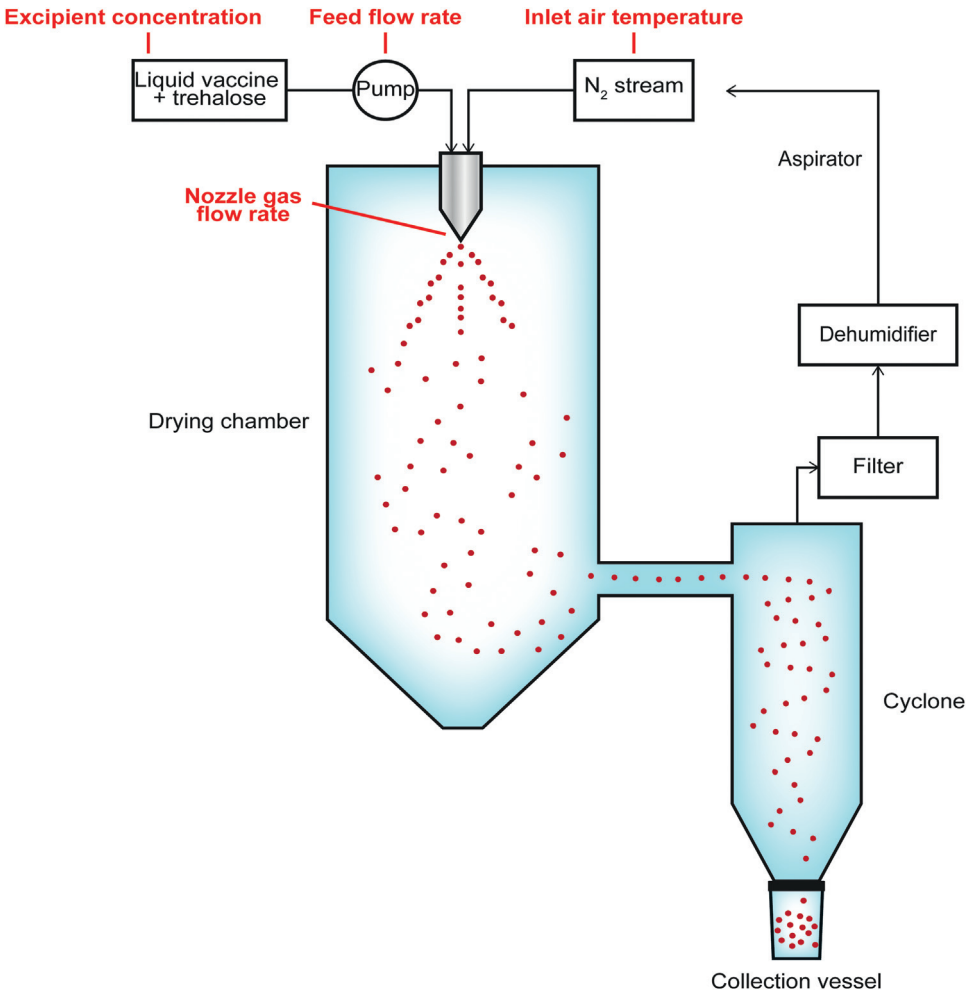

Fig. 1. Spray drying process: A liquid influenza vaccine (whole inactivated influenza virus vaccine) was spray dried with trehalose as an excipient to produce a powder vaccine. Investigated process parameters are indicated in red. Aspirator capacity was kept fixed at 22 m^3_n/h (highest aspirator setting possible).

the size of the spray drier and airflow rate, the drying may take between 0.2–30 s (Anon., 1999). During drying, the protein in evaporating droplets may experience reversible or irreversible denaturation. This could be due to the loss or weakening of hydrogen bonds and simultaneous increase in hydrophobic interactions during evaporation of water. However, the self-cooling effect of droplets due to water evaporation prevents the temperature increase of the droplet surface above the wet bulb temperature (temperature of drying aerosols achieved through evaporation cooling) (Katja, 2011). Thus, spray drying may be an appropriate procedure for drying thermolabile vaccines and has been used to produce experimental dry powder vaccines against measles (Lin et al., 2011; Ohtake et al., 2010), influenza (Lovalenti et al., 2016; Saluja et al., 2010; Scherliess et al., 2014; Sou et al., 2015), tuberculosis (Wong et al., 2007) and hepatitis B (Chen et al., 2010). Moreover, dry powdered measles vaccine has showed promising results in phase 1 clinical trials (MVDP author group et al., 2014). Therefore, spray drying might be a suitable alternative method to obtain dry powders of a variety of vaccines (Amorij et al., 2008).

The spray-drying process used to produce these powders with desired product characteristics is usually optimized by a one-factor-at-a-time (OFAT) approach, where the effect of process parameters on the product are assessed in a linear fashion, one-at-a-time. This consumes a lot of time and resources. Moreover, it requires a large number of experiments and interactions between parameters are frequently missed. A Design of Experiments (DoE) approach can be used instead in order to systematically screen and optimize processes. DoE is a structured approach that can be used to identify critical and non-critical parameters, and their respective interactions, of a production process. Moreover, it can be used to quantify the impact of raw materials and process parameters on the product characteristics and quality (Cook et al., 2013). Several studies have employed a DoE approach to investigate and optimize the spray drying process of proteins (Prinn et al., 2002; Maltesen et al., 2008) and liposomal adjuvants (Ingvarsson et al., 2013). However, the potential of utilizing DoE for producing spray-dried powder vaccines has not been explored so far.

To maintain the structural integrity during and after the drying process, biological products such as proteins or vaccines often require excipients that act as stabilizers in their formulation. The sugar trehalose is an excipient commonly used for stabilizing vaccines, due to its good protein-stabilizing characteristics (Geeraedts et al., 2010; Ogain et al., 2011). Including trehalose in the vaccine formulations for spray drying might therefore be essential to obtain a stable vaccine product after spray drying. Previously, spray drying of influenza vaccines has been described using various sugars, Maa et al. (Maa et al., 2004) were first to describe the use of trehalose, Sou et al. (2015) combined trehalose with leucine, whereas Scherliess et al. (2014) showed the