Chapter 14
Powder Vaccines for Pulmonary Delivery

Tom Jin and Eric Tsao

Abstract Spray drying represents an elegant one-step process for generating powder products with unique particle characteristics. Respiratory delivery of powder vaccines for the prevention of infectious diseases has shown great promise. Pulmonary delivery using powder vaccine aerosols is an approach to immunization that offers advantages over the use of injection in terms of both delivery technology and vaccine formulation. Powder vaccines for needle-free delivery have been successfully produced during the past decade. The essential elements for the preparation of a powder vaccine through spray drying are reviewed in this chapter. For example, the screening of formulations, the spray dryers from laboratory scale to aseptic manufacturing facilities, and the selection of dry powder inhalers (DPIs) for pulmonary delivery. The advantages and challenges of manufacturing powder vaccines are also discussed.

14.1 Introduction

Current vaccines are generally administered via the intramuscular (i.m.) or subcutaneous (s.c) route using needles and syringes. Despite its common use, needle-based immunization has several disadvantages. In the developing world, there are major challenges of disease transmission through reuse of needles. Not limited to hepatitis B and C, human immunodeficiency virus, or other viruses, the infections through the needle penetration injuries increase the economic burden on health care systems. The World Health Organization (WHO) claims that up to 30 % of regular needle injections are considered unsafe [1]. Organizations such as the WHO, The Centers for Disease Control (CDC), and groups such as The Gates Foundation have supported the development of needle-free alternatives, particularly for vaccine

T. Jin (✉)
Aeras, Rockville, MD, USA
e-mail: zjin@aeras.org

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delivery. The search for the methods of vaccine delivery not requiring a needle and syringe has been accelerated by recent concerns regarding pandemic disease, bioterrorism, and disease eradication campaigns. Needle-free vaccine delivery could aid in mass vaccinations by increasing the ease of use, speed of delivery, and by offering improved safety, compliance, decreased costs, and reduced pain associated with vaccinations.

Over the past decade, numerous vaccine delivery technologies have emerged, of which several are powder-based methods. These include microspheres for long-acting delivery, fine powders for pulmonary delivery, and biopharmaceutical/vaccine powders for intradermal delivery. Pulmonary delivery using powder vaccine aerosols is an approach to immunization that offers advantages over injection in terms of both delivery technology and vaccine formulation. The technology advantages include increased safety and ease of administration. The formulation advantages when using dry powders are the potential reduction of refrigeration requirements, and increased stability during transport and administration, thereby facilitating mass vaccination. Additionally, there is a potential for enhanced biological efficacy since pulmonary delivery may produce mucosal immunity superior to that which is produced after parenteral vaccine administration.

Spray drying, the process wherein a liquid feed is rapidly transformed into a dried particulate form by atomizing into a hot drying medium (air, nitrogen, or CO_2 gas), is a common method for preparing solids in the chemical, food, and pharmaceutical industries. It has been recommended as an alternative to freeze drying for the preparation of inhalation products, as it represents an elegant one-step process for producing biopharmaceutical formulations with unique particle characteristics. Spray drying has the additional advantage of being a faster and more cost-effective dehydration process than freeze drying. Vaccine powder formulations suitable for needle-free injection can be successfully produced by spray drying [2–4].

Pulmonary delivery of spray dried pharmaceutical products became the route of choice after the introduction in 1967 of dry powder inhalers (DPIs) to treat patients with asthma [5]. The spray drying technique being applied in vaccine development is relatively new compared to freezing drying technology. Published studies of powder vaccines are listed in Table 14.1 [6–11]. Respiratory delivery of powder vaccines for prevention of infectious diseases has shown great promise. Klas et al. reported that a single immunization with a dry powder anthrax vaccine could protect rabbits against lethal aerosol challenge. The Rhesus Macaques test showed that a dry powder measles vaccine induced robust measles virus-specific humoral and T-cell responses, without adverse effects, which completely protected the macaques from infection with wild-type virus more than one year later [6]. A clinical trial of measles vaccine is in development in India [12].

Although powder formed vaccines have shown many benefits compared to liquid forms, including increased safety of administration, storage stability, and biological efficacy, the development of methods for production of powder vaccines are still in their infancy. Several practical challenges need to be addressed before powder vaccine production can be scaled up, ultimately to meet the needs of mass vaccination. For example, optimization of formulations to generate less

Table 14.1 Current status of spray dried vaccines

Vaccines	Classification	Development status	References
Measles	Live attenuated	Preclinical	[6]
BCG	Live attenuated	Preclinical	[2]
Influenza	Subunit	Preclinical	[7]
	Split	Clinical phase I	[8]
	Whole inactivated	Preclinical	[9]
Anthrax	Subunit (*r*PA + conjugated peptide)	Preclinical	[10]
Plague	Subunit (F1-V)	Preclinical	[11]

hygroscopic particles with a more suitable size range (usually 1–5 μm) for pulmonary delivery and powder filling, and development of economic DPIs.

14.2 Formulations

The most commonly used method to stabilize biological ingredients, such as proteins, vaccines, and gene delivery systems, is to convert them to dry cakes or powders. The stability of dried formulations is believed to be related to lack of mobility of the biopharmaceutical components in the dried form, and the absence or reduction of certain degradation pathways such as hydrolysis. However, depending on the drying method, freezing and/or drying stresses may affect the structural integrity and/or activity of a dry powder vaccine. Accordingly, drying formulations using appropriate stabilizers are required for preservation of these properties. Unfortunately there is no definitive formulation that can be applied to all products. The most common excipients in formulation screening studies are classified as follows: (1) Carbohydrates, such as trehalose, mannitol, dextrans, sucrose, and myo-inositol; (2) Amino acids, such as leucine, histidine, and arginine; (3) Proteins, such as human serum albumin; (4) Polymers, such as polyvinylpyrrolidone (PVP); and (5) Buffer agents, such as PBS and histidine. Formulation screening of a powder vaccine can be time-and-labor consuming, and typically follows a trial and error process. Fortunately, there are various modern instruments that can be used to accelerate this process, such as differential scanning calorimetry (DSC), scanning electron microscopy (SEM), X-ray diffraction, and laser diffraction.

Disaccharides are amongst the most frequently used excipients, with trehalose being a particularly common selection. Trehalose has been shown to have the ability to protect active ingredients during the spray drying process and to result in improved stability in long-term storage [13–19]. However, trehalose and sucrose-based powders are more hygroscopic than other excipients, absorbing moisture during handling in the laboratory environment leading to degradation in physical properties of the powder and reduction in the ease of dispersion [4]. The sensitivity of powders to moisture uptake is important because the aerosol physical properties of inhalable dry powders are strongly dependent on moisture content; too

much water can cause particle agglomeration, leading to reduced respirability. One compromise is to combine trehalose with other less hygroscopic components, such as mannitol and leucine. Sievers et al. reported a dry powder vaccine of Alum-HBsAb containing sufficient amounts of stabilizing trehalose. The powder did not lose potency after it was stored for 43 days at either −20 °C or 66 °C, and testing in mice showed full retention of immunogenicity [20].

Leucine- and mannitol-based formulations are less hygroscopic and have been used for TB powder vaccine [2, 4]. Mannitol is stable as a powder and resists moisture resorption at relatively high humidities. These characteristics make it an ideal substance to encapsulate biopharmaceuticals for inhalation, for diagnostic and therapeutic purposes. The inhalation of dry powder mannitol alone has been shown to cause a marked increase in MCC (mucociliary clearance) in the whole right lung and in all lung regions, in both asthmatic and healthy subjects. Inhalation of dry powder mannitol was well tolerated by all subjects and induced only a mild cough which was reproduced on the control day [21–26]. This increases the advantage of using a mannitol-based spray drying formulation in the development of powder form vaccines. Jin et al. reported that a TB vaccine prepared with mannitol-based formulations, which also contained small and high molecular weight sugar stabilizers (trehalose and two dextrans), successfully resisted water absorption. The spray-dried TB vaccine could be stored at 4 °C and 25 °C for 12 months without any significant change in vaccine potency. After storage at 37 °C for 5 weeks, the loss of virus activity was only 0.12 log [4]. The combination of excipients achieved optimization of viral processing and storage stability, while mitigating the negative particle forming properties of trehalose.

Immobilization of the labile materials in amorphous glass is believed to be advantageous to maintain the activity of the incorporated molecules [27]. Resistance to crystallization can be evaluated by measuring the glass transition temperature (T_g), which is the temperature at which the transition from a glassy to a rubbery state or from a low molecular mobility to a high molecular mobility (and therefore, higher risk of crystallization) occurs. PVP and albumins are known to increase T_g, which means that formulations containing these can be exposed to higher ambient temperatures before the glass transition occurs [15, 28, 29]. However, PVP alone as a stabilizer in a formulation of attenuated live Newcastle disease vaccine virus did not appear to prevent loss of virus activity during the spray drying process, and required the use of other stabilizers, such as trehalose and albumin [16].

Dextrans have a long history of being used as excipients in vaccine formulations. They have been shown to prevent crystallization during the spray drying or freeze drying processes [30, 31]. Lung delivery of aerosolized dextran is well tolerated and has potential therapeutic benefit in the treatment of cystic fibrosis [32]. Dextran has a high T_g value of −9 °C. A formulation containing dextrans has been shown to increase the T_g of trehalose from 50.55 to 97.09 °C. The formulation also generates a dry powder that inhibits recrystallization of stabilizing sugars, preventing inactivation of incorporated labile materials [4]. In formulations with a T_g occurring at about 50 °C and higher, the powders and microparticles should be physically stable at temperatures up to about 40 °C, as long as the powders are protected from

moisture ingress. A higher T_g value of a formulation usually suggests enhanced long-term thermostability.

Formulation development is essential for a powder vaccine. Jin et al. showed that powder formulation helped stabilize an adenovirus 35-vectored tuberculosis (TB) vaccine so that variations in temperature did not negatively impact its effectiveness or shelf life [4]. They demonstrated that it is possible to produce a stable dry powder formulation of a TB vaccine suitable for mass vaccination in a one-step drying process. The process of identifying and optimizing key excipients directly relates to the recovery of active ingredients, the yield of powder product, and stability during storage. The following properties could be used to evaluate formulation development during or post-spray drying activities: (1) High recovery for both active ingredient and powder; (2) Formulation has relatively high T_g for good stability during storage; (3) Less hygroscopic powder could benefit both vaccine stability and powder filling process; (4) Narrow size distribution (2–5 μm) and good aerosolization characteristics of final product provide easy delivery to the deep lung parenchyma by DPIs.

14.3 Spray Drying: From Concept to cGMP Products

One of the oldest forms of industrial drying is spray drying. A patent from 1872 by Percy gives probably one of the first detailed descriptions of drying of sprays [33]. With the advancement of science and technology, pulmonary delivery of drugs has become the route of choice after the introduction of the DPI in 1967 [5]. The application of spray drying in vaccine development has only occurred in the last decade (Table 14.1). Different types of powder vaccine are in the preclinical and clinical phases. As previously mentioned, the first needle-free measles vaccine clinical trial is going to be initiated in India, using the measles powder vaccine developed by Dr. Sievers of the University of Colorado.

Spray dryers designed for cGMP vaccine production have not been fully developed. The requirements for this process are that it needs to be inexpensive, scalable, GMP-compliant, and capable of sterile manufacturing from beginning to end. Most researchers in the early stages use the Mini Spray dryer B-290 (Büchi, Switzerland) in their laboratory scale processes. The sources for "real" aseptic cGMP spray dryers are limited. The manufacturers SPX Anhydro and GEA Niro claimed that they had developed spray dryers for cGMP manufacturing of powder vaccine. One of these cGMP spray dryers, the MS-35 (SPX Anhydro), was set up in the facility of Aeras. It was custom designed by Anhydro for manufacturing of TB vaccines and other powder form products. The MS-35 meets the FDA requirement of the aseptic concept for the manufacturing of human vaccines. When the optimum parameters were selected, the output of MS-35 could reach 180 ~ 250 g of powder within 4 h (Table 14.2). The differences in output between the Büchi B-290 and MS-35 are listed in Table 14.3. The scaled up process using the MS-35 increased recovery by 20 % points, with a fourfold increase in powder yield in the final product.

Table 14.2 Output of MS-35 (Anhydro) cGMP spray dryer

Vaccine	Spray drying period/lot	Yield* (g)	Dosages/lot (10 mg/dosage)
Bacteria/virus (Live)	2~4 hr	180	18,000
Protein/peptide	2~4 hr	250	25,000

*Yield is the powder mass collected at the end of each run.

Table 14.3 Process comparison between laboratory and cGMP spray drying

	Recovery (%)	Particle size (μm)	Feeding rate (mL/min)	Yield (g/hr)
B-290 (Büchi)	50~65	3~4	3~5	15
MS-35 (Anhydro)	70~85	2~3	10~12	60

Table 14.4 Comparison of cost-effectiveness between spray drying and lyophilization

	Process time	Labor	Materials	Consumables (process gases/ electricity/cooling water)	Equipment	Output dosages* (250g solid)
Spray drying (MS-35)	2~4 h	Comparable	Comparable	$300	Comparable	10,000
Lyophilizer (Shelf area in 40 SF)	2~72 h	Comparable	Comparable	$300	Comparable	10,000

*25mg/dose or vial; 0.5 ml filling for lyo vial; 25 mg for powder product.

The smaller particle size with the MS-35 might be caused by the more effective and even evaporation with this spray dryer. A comparison of the cost-effectiveness of spray drying vs. lyophilization showed promising results: tenfold shorter processing cycle and larger evaporative capability than traditional lyophilization (Table 14.4). They are comparable in other factors relating to cost-effectiveness between the MS-35 and the lyophilizer (40 SF shelf area). Although spray drying has been successfully used in the production of food and biochemical products, use of the technology in the manufacture of human vaccines needs to consider the following additional challenges: (1) Low inlet temperature is required to avoid denaturation or inactivation of proteins or live active ingredients during the drying process, which will compromise the output of final products caused by reduced feeding rate; (2) Aseptic design for the spray dryer used in powder vaccine production is strictly required by FDA, which usually is not a concern in food, biochemical, and pharmaceutical industrials; (3) Requirement for large scale and accurate powder filling, and (4) Effective and economic DPIs need to be developed and marketed.

14.4 Dry Powder Inhalers

There are two major types of DPIs: unit-dose devices and reservoir-type multiple-dose devices. Powder vaccine could only employ a single dosage device for individual subjects, even in mass population vaccinations. Since the inception of the first DPI Spinhaler® (Aventis), device technology has continued to grow and a lot of devices are now currently available on the market, such as Aerolizer®, Diskus®, Flexhaler®, Handihaler®, Rotahaler®, Turbuhaler® and Twishaler®.

The airborne product generated by a powder inhaler should contain a significant proportion of particles less than 5 μm in size. In order for a powder to be suitable for pulmonary delivery, the aerodynamic size requirements are that particles must be in the 1–5 μm range (Fig. 14.1). PuffHaler, a dry powder device from ActivDry (Fig. 14.2), has been applied in the measles powder immunization and challenge study in rhesus macaques reported by Dr. Griffin [6]. The device consists of three components: the vaccine formulation held in an aluminum foil blister, the reservoir, and the dispersion mechanism to generate aerosols. When the PuffHaler squeeze bulb is compressed to 2 psi, the silicone rubber burst valve pops open. The air rushes into the disperser through the powder in the aluminum foil blister and the aerosol cloud fills a collapsed plastic bag reservoir. The aerosol-filled bag is detached and affixed to a facemask from which the subject is allowed to breathe for 30 s to become vaccinated. As a control, a dry powder device of BD Solovent (BD Technologies) (Fig. 14.3) was also evaluated in this study. The syringe of the BD Solovent device is used to pressurize the capsule containing the powder vaccine. As the pressure rises, the thin films sealing the capsule abruptly rupture, and the powder is expelled and captured in the disposable spacer for delivery through a silicone facemask. The study demonstrated that both the PuffHaler and Solovent devices efficiently delivered the vaccine to the deep lung, resulting in more robust antibody and T-cell responses than nasal delivery or s.c. injection of the live attenuated measles vaccine.

The inhalation route offers an enormous absorptive surface area, in the range 35–140 m^2, of thin (0.2 μm) and highly vascularized epithelium, which leads to high bioavailability. Direct delivery of drug into the deep lungs utilizing the patient's respiration is increasingly being explored as a mechanism for the delivery of systemic drugs. Successful delivery of vaccines into the deep lungs depends on the integration between powder formulations and the device performance [34, 35]. Licensing and marketing approval requires that current DPIs demonstrate in vitro performance and in vivo efficacy and reliability. However, the mass of vaccine delivered and the aerodynamic particle size can change, depending on the characteristics of inhalation. Hence, one approach to developing successful DPIs is to decrease the dependence of these devices solely on the subject's inhalation.

Among aerosol generation systems, DPIs present several advantages. They are propellant-free, portable, easy to operate, and low-cost devices with improved stability of the formulation as a result of the dry state. The challenge of any

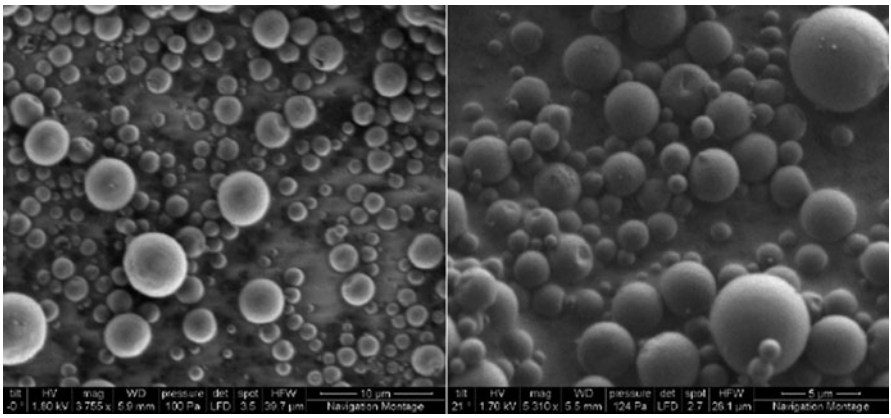

Fig. 14.1 The SEM images of Aeras 402 powder vaccine

Fig. 14.2 A dry powder device, PuffHaler, from ActivDry

inhalation delivery system is, however, to generate particles with an adequate range of particle sizes. In the case of dry powders, this is greatly impeded by particle aggregation which lowers the fraction that is respirable, i.e., the fraction of particles (and particle aggregates) with an aerodynamic diameter $\leq$5 μm.

Efficient delivery of vaccines from DPIs depends not only on the device, but also on drug formulation and the production of suitable powders for effective respiratory

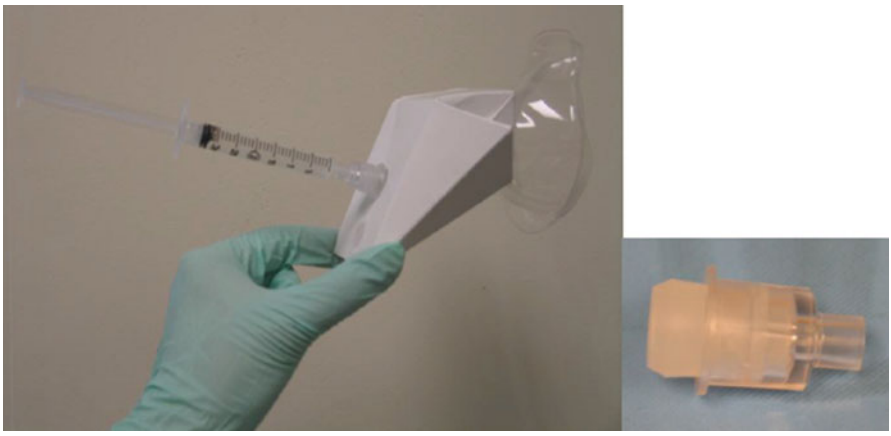

Fig. 14.3 A dry powder device, Solovent, from BD Technologies**.** The right figure is the enlarged photo of capsule containing powder vaccine, sealed by thin film at two ends

deposition as well as formulation of powders with or without excipients. To realize the full potential of DPIs, at the lowest cost to both vaccine companies and the recipient populations, innovation of new devices with enhanced lung deposition and reliability will play important roles in the future.

14.5 Conclusions

In conclusion, spray drying as a new technology being applied in vaccine development has shown promising results. Needle-free pulmonary vaccine delivery could aid in mass vaccinations by increasing ease and speed of delivery, and by offering improved safety and compliance, decreased costs, and reduced pain associated with vaccinations. In addition, aerosol delivery of powder vaccine has the potential for increased protection by direct stimulation of immunity in the lung compared to vaccines delivered by the parenteral route. There are three essential aspects that need to be fully investigated for the application of spray drying to vaccine development: (1) Optimum formulation for each individual vaccine, which is closely related to good stability, less hygroscopicity, and prompt powder filling of final product; (2) Aseptic design in a cGMP spray dryer; and (3) Economic and efficient DPIs to permit mass vaccinations.

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