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Review

Drug/polymer nanoparticles prepared using unique spray nozzles and recent progress of inhaled formulation

Tetsuya Ozeki[*], *Tatsuaki Tagami*

Drug Delivery and Nano Pharmaceutics, Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya, Aichi 467-8603, Japan

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ABSTRACT

Inhaled formulations are promising for pulmonary and systemic non-pulmonary diseases. Functional engineered particles including drugs and drug-loaded nanocarriers have been anticipated because they can improve drug delivery efficacy against target sites in the lungs or blood. In this review, unique spray nozzles (e.g., four-fluid spray nozzle and two-solution mixing type nozzle) for the preparation of nanocomposite particles which mean microparticles containing drug nanoparticles are described. These nozzles can produce nanocomposite particles in one-step and their spray drying system is suitable for scaling-up. Nanocomposite particles are useful in improving drug absorption and delivery efficacy against alveolar macrophages. In addition, recent studies on several pulmonary diseases (tuberculosis, lung cancer, cystic fibrosis, pneumonia, vaccine and others) and related inhaled formulations were also reviewed.

1. Introduction

Pulmonary drug administration has the potential of a non-invasive and easy administration method. It has attracted much attention in the field of pulmonary and non-pulmonary diseases for decades because of the specific structure and function of lung tissue; the lungs have large surface area, thin mucosal cell membrane, and blood vasculature. Alveoli, which are the site of oxygen and carbon dioxide exchange, contain blood capillaries at high density. In addition, drugs can easily penetrate the thin layer of alveolar endothelial cells and enter the blood. Compared with the oral administration, pulmonary administration avoids the hepatic metabolism, which is known as first-pass effect. Moreover, the lungs contain lymph nodes and present immune competent cells. Therefore, various drugs and vaccine delivery systems targeting the lungs have been developed.

Currently, both liquid aerosol and dried powder formulations have been used in pulmonary administration and some

* *Corresponding author*. Tel.: +81 52 836 3463; fax: +81 52 836 3464.
E-mail address: ozekit@phar.nagoya-cu.ac.jp (T. Ozeki).
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devices for inhalation have been recently reviewed [1]. Additionally, the recently approved products of inhaled formulation was summarized in Table 1. Although the administration of aerosol by nebulizer has been established, dried formulation is superior to liquid aerosol from the stability perspective. However, the diameter of the dried powder should be controlled. The optimization of aerodynamic diameter is necessary to achieve delivery into deeper regions such as the alveoli [2]. In addition, the change in the surface morphology can affect the aerodynamic diameter, and porous and wrinkled particles have been developed [3].

In this review, two special spray nozzles were introduced. Spray nozzles have been established to prepare drug "nanocomposite particles", which are microparticles containing drug nanoparticles. These composites are useful for the preparation of inhaled formulations against pulmonary and systemic non-pulmonary diseases. Moreover, recent studies focusing on inhaled drug formulations with or without drug carriers were reviewed.

2. One-step preparation of nanocomposite particles by spray dryer equipped with special spray nozzles

The pulmonary administration has recently been anticipated to improve the absorption of poor water-soluble drugs. Approximately 40% of potential therapeutic compounds are water-insoluble compounds that are classified as biopharmaceutics classification system (BCS) class 2 or 4. A common method for improving drug absorption is the size reduction of bulk drugs (e.g., nanoparticles drugs), which could enhance their solubility because of the increase in their surface area. Furthermore, nanoparticle drugs could be more easily absorbed into the blood.

However, the beneficial properties of nanoparticles are often easily lost by self-agglutination and their redispersion is very difficult. The prevention of self-agglutination is an important issue and some solutions have been developed, such as reducing their dimensions to the order of microns, which means the preparation of nanocomposite particles. In our group, nanocomposite particles have been prepared using a spray dryer equipped with a unique spray nozzle.

Table 1 – Recent product of inhaled formulations in the market.

Name	Drug	Category	Device
Alvesco®	Ciclesonide	Steroid	pMDI
Asmanex®	Mometasone	Steroid	DPI
Adoair®	Fluticasone and Salmeterol	Combination	pMDI
Symbicort®	Budesonide and Formoterol	Combination	DPI
Oxis®	Formoterol	LABA	DPI
Onbrez®	Indacaterol	LABA	DPI
Spiriva®	Tiotropium	LAMA	SMI
Seebri®	Glycopyrronium	LAMA	DPI
Afrezza®	Insulin	Diabetes	DPI

Abbreviation: pMDI: pressurized metered-dose inhaler, DPI: dry powder inhaler, SMI: soft mist inhaler, LABA: long-acting beta agonist, LAMA: long-acting muscarinic antagonists.

Four-fluid spray nozzle is a unique spray nozzle containing two liquid passages and two air passages (Fig. 1) (Fujisaki Electric Co.; http://www.fujisaki-hest.com). Compressed air is flown from the air passages to transform solutions into mist. The solution flown in the passages is mixed with compressed air and the solution is accelerated. The collision of the compressed air at the end of the nozzle generates a shockwave that transforms the solution into single micron mist. The single micron mist is quickly and efficiently dried because of its reduced size and increased surface area. For example, poor water-soluble drugs are dissolved in an organic solvent and the solution is flown in one passage. Then, mannitol (MAN) aqueous solution is flown into the other passage. The drug-organic mist and MAN-aqueous mist are mixed at the end of the nozzle, where the drug starts crystallizing by anti-solvent effect, which is the phenomenon in which solubility change induces the precipitation of the drug. The drug/MAN mist is immediately spray-dried until the drug crystallization has been completely progressed. Thus, relatively small drug nanoparticles are produced in MAN microparticles. Because one-step preparation and large amount of nanocomposite particles can be obtained by spray drying, the method is suitable for scaling-up. In previous studies, composites of flurbiprofen/salicylate [4], polymer/MAN [5], rifampicin/MAN [6], and rifampicin/polymer/MAN [7] were developed using the spray dryer equipped with a four-fluid spray nozzle.

Although the four-fluid spray nozzle is useful in the one-step preparation of nanocomposite particles, optimization of spray drying conditions has been sometimes necessary, and it has been unclear if the anti-solvent effect occurred efficiently. Therefore, a two-solution mixing type nozzle has been developed to prepare nanocomposite particles (Fig. 2) (Ohkawara Kakohki Co.; http://www.oc-sd.co.jp/english/index.html). In this device, similar to the four-fluid spray nozzle, the two solutions are separately flown in different passages and are mixed in the mixing chamber in the nozzle. The drug solution dissolved in organic solvent is added into the MAN-aqueous solution in the mixing parts and the mixture is immediately spray-dried. Anti-solvent effect properly occurs in the mixing parts of the nozzle, and we speculate that the preparation of the nanocomposite particles is achieved in suitable conditions. The spray nozzle is customizable and some parts of it can adjust the mixing condition. Ethylcellulose (EC) is a poor water-soluble polymer, which was used as the model compound; EC/MAN composite was prepared using a spray dryer equipped with the two-solution mixing type spray nozzle [8]. The composite particles prepared with this method exhibited relatively small diameter compared with those prepared using the four-fluid spray nozzle. To extend our study, microparticles containing solid dispersion drug nanoparticles were prepared [9]. Solid dispersion is a technique used to increase drug dissolution and absorption. Solid dispersion of nanoscale drugs showed enhanced intestinal absorption compared with composites containing drug nanoparticles and original drug powders. Although a detailed investigation about on the inner structure, crystallinity, and physical stability of microparticles is required in the study, these unique nanocomposite particles are promising formulations to enhance the absorption of poor water-soluble drugs.