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# Fabrication of nanocomposite particles using a two-solution mixing-type spray nozzle for use in an inhaled curcumin formulation

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A B S T R A C T

A unique two-solution mixing-type spray nozzle is useful for producing nanocomposite particles (microparticles containing drug nanoparticles) in one step. The nanocomposite particles can prevent nanoparticle aggregation. Curcumin has many reported pharmacological effects. Curcumin was entrapped in mannitol microparticles using a spray dryer coupled with a two-solution mixing-type spray nozzle to prepare "curcumin nanocomposite particles" and the application of these particles for inhalation formulations was investigated. Spray drying conditions (flow rate, concentration and inlet temperature) affected the size of both the resulting curcumin nanocomposite particles and the curcumin nanoparticles in the nanocomposite particles. The aerosol performance of the curcumin nanocomposite particles changed depending on the spray drying conditions and several conditions provided better deposition compared with the curcumin original powder. The curcumin nanocomposite particles showed an improved dissolution profile of curcumin compared with the original powder. Furthermore, the curcumin nanocomposite particles showed a higher cytotoxic effect compared with the curcumin original powder towards three cancer cell lines. Curcumin nanocomposite particles containing curcumin nanoparticles show promise as an inhalation formulation for treating lung-related diseases including cancer.



## 1. Introduction

Curcumin is extracted from the Indian spice turmeric and has been extensively studied due to its various pharmacological effects, which include anti-oxidant, anti-inflammatory (Menon and Sudheer, 2007), monoaminergic, immune-modulating, neuro-protective (Cole et al., 2007; Lopresti et al., 2012), anti-microbial (Moghadamtousi et al., 2014), anti-angiogenic and anti-cancer effects (Agrawal and Mishra, 2010). Curcumin is a natural inhibitor of NF-κB, cyclooxygenase-2, and lipooxygenase, and inducible nitric oxide synthase (Bengmark, 2006; Menon and Sudheer, 2007). Curcumin is safe and gram doses are tolerated by patients (Anand et al., 2007; Fan et al., 2013). Thus, the multiple-effects of curcumin have led to its use to treat various diseases, including bowel disease (Baliga et al., 2012; Hanai and Sugimoto, 2009), Alzheimer disease (Chin et al., 2013), Parkinson disease (Mythri and Bharath, 2012), depression (Tizabi et al., 2014), wound healing (Akbik et al., 2014), cardiac diseases (Katanasaka et al., 2013) and various kinds of cancers (Bandyopadhyay, 2014). Curcumin has also been used to treat airway inflammation and to slow the progress of lung cancer (Moghaddam et al., 2009) and cigarette smoke-induced pulmonary emphysema (Suzuki et al., 2009). However, the major drawback of curcumin is its poor intestinal bioavailability (Anand et al., 2007); in addition, curcumin is degraded in the serum, resulting in very low accumulation in lung tissues. Consequently, systems for delivering curcumin specifically to targeted sites are being developed.

Inhalation formulations are being developed to treat lung-related diseases. Both the lungs and the intestine have large surface areas and are equally useful for absorbing drugs. Inhalation formulations are superior to oral formulations for delivering drugs to treat pulmonary diseases because inhaled formulations directly and rapidly deliver the drug to the disease site in lung tissue, whereas only a very low percentage of an oral formulation is delivered to the disease site. Particle engineering allows control of the size, shape and porosity of inhalation formulations and is important for delivering the drug efficiently to the target site. For example, particle sizes in the range 1 μm–3 μm are suitable for deposition in the deeper regions of lung tissue, such as the alveolar region (Edwards et al., 1998). Furthermore, reducing the size of the

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drug particles aids the bioavailability of poorly water-soluble drugs because smaller drug particles can increase drug dissolution (Ozeki and Tagami, 2013). Nanosized poorly water-soluble drugs can provide advantageous properties for both inhalation and oral formulation (Bailey and Berkland, 2009). Inhalation therapies are typically used to treat asthma, chronic obstructive pulmonary disease, and diabetes. Inhaled therapy to treat lung cancer is promising, although inhaled cancer therapies require increased safety measures to protect both patients and medical staff compared to non-inhaled therapies (Zarogoulidis et al., 2012).

A two-solution mixing-type spray nozzle has been developed for the one-step preparation of nanocomposite particles, which are microparticles containing poorly water-soluble nanoparticles (Ozeki et al., 2012) (Fig. 1). The key to producing nanocomposite particles using a nozzle is to combine spray drying and precipitation. An organic solution containing the poorly water-soluble drug and an aqueous solution containing a water-soluble sugar alcohol (or sugar) as a filler are mixed in the nozzle, producing nanosized drug crystals as the solvent composition changes. The mixture is immediately sprayed and dried before crystal growth is complete, leading to the formation of nanocomposite particles. We previously reported that nanocomposite particles containing drug nanoparticles exhibited improved intestinal bioavailability (Nishino et al., 2012). Nanocomposite particles produced in a cyclone spray dryer are approximately single-digit micron in diameter, so nanocomposite particles produced using a two-solution mixing-type spray nozzle used in conjunction with a cyclone spray dryer may be useful for producing inhalation formulations.

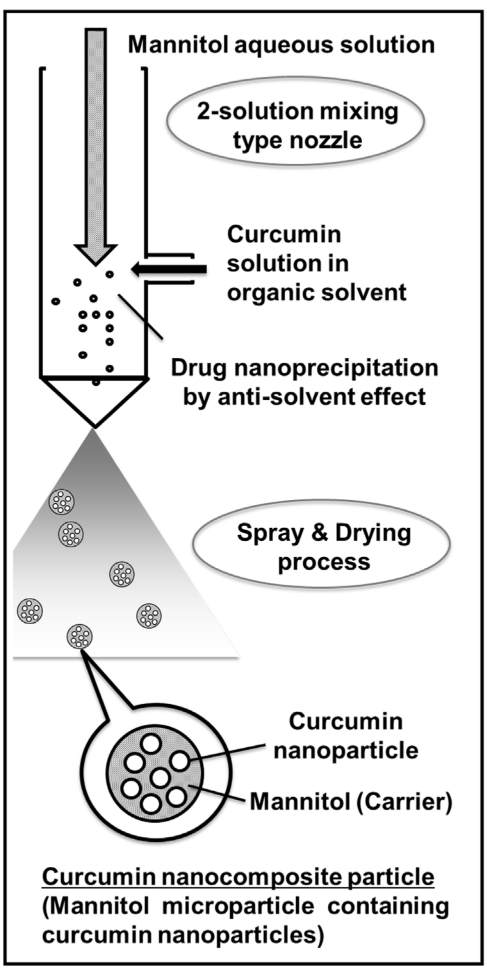


**Fig. 1.** Schematic of the one-step preparation of curcumin nanocomposite particles using a two-solution mixing-type nozzle. Curcumin nanocomposite particles which mean mannitol microparticles containing curcumin nanoparticles were prepared by changing the spray drying conditions in Table 1 and in the Materials and Methods section.

In this study, we prepared curcumin nanocomposite particles as an inhalation formulation using a two-solution mixing-type nozzle together with a spray dryer. The pharmacological effect of curcumin should make this formulation useful for treating inflammatory lung diseases and lung cancer. Particle engineering of nanocomposite particles using a spray dryer could enhance drug delivery and efficacy. We therefore investigated the effect of different experimental spray drying conditions on the resulting curcumin nanocomposite particles prepared and their effect on the curcumin formulation.

## 2. Materials and methods

### *2.1. Reagents*

Curcumin was purchased from Sigma Aldrich (St Louis, MO, USA). Mannitol was kindly provided by Mitsubishi Shoji Foodtech Co. (Tokyo, Japan). Organic solvents were of analytical grade.

### *2.2. Preparation of curcumin nanocomposite particles using a two-solution mixing-type spray nozzle*

Curcumin nanocomposite particles were prepared using a Twin Jet Nozzle RJ10 TLM1 spray dryer equipped with a two-solution mixing-type spray nozzle (Ohkawara Kakohki Co. Ltd.; Yokohama, Japan) under various experimental conditions, as shown in Table 1. Specifically, the flow rate (kg/h) of mannitol and curcumin, the concentration (%) of mannitol and curcumin, and the inlet temperature were systematically changed. The mannitol was dissolved in water and curcumin was dissolved in acetone/methanol (2/1, v/v). Individual solutions were introduced into the nozzle through separate tubes and mixed in the nozzle. The mixture was immediately spray dried with air from a compressor and heated in the cyclone dryer. The resulting powder was collected and immediately placed in a desiccator until use.

### *2.3. Evaluation of curcumin nanocomposite particles and curcumin nanoparticles*

The appearance of the curcumin nanocomposite particles was observed using a scanning electron microscope (SEM, S-4300; Hitachi, Tokyo, Japan). The Feret diameter of each particle was measured from the images (n > 300) and the median particle diameter was obtained. The diameters of curcumin nanoparticles in curcumin nanocomposite particles cannot be measured directly;

**Table 1**
Experimental conditions tested using a spray dryer and two-solution mixing-type nozzle.

| Condition | Inlet Temp (°C) | Flow rate (kg/h) | | Concentration (%) | |
|---|---|---|---|---|---|
| | | Mannitol | Curcumin | Mannitol | Curcumin |
| a | 200 | 0.72 | 0.24 | 1.5 | 0.35 |
| b | 200 | 0.72 | 0.24 | 1.5 | 0.18 |
| c | 200 | 0.72 | 0.24 | 1.5 | 0.09 |
| d | 200 | 0.72 | 0.48 | 1.5 | 0.35 |
| e | 200 | 0.72 | 0.12 | 1.5 | 0.35 |
| f | 200 | 0.72 | 0.24 | 3 | 0.35 |
| g | 200 | 0.72 | 0.24 | 5 | 0.35 |
| h | 145 | 0.72 | 0.24 | 1.5 | 0.35 |
| i | 175 | 0.72 | 0.24 | 1.5 | 0.35 |
| j | 200 | 0.5 | 0.24 | 1.5 | 0.35 |
| k | 200 | 0.9 | 0.24 | 1.5 | 0.35 |
| l | 200 | 0.9 | 0.13 | 20 | 4.2 |