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Historical perspective

Advantages and challenges of the spray-drying technology for the production of pure drug particles and drug-loaded polymeric carriers

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ABSTRACT

Spray-drying is a rapid, continuous, cost-effective, reproducible and scalable process for the production of dry powders from a fluid material by atomization through an atomizer into a hot drying gas medium, usually air. Often spray-drying is considered only a dehydration process, though it also can be used for the encapsulation of hydrophilic and hydrophobic active compounds within different carriers without substantial thermal degradation, even of heat-sensitive substances due to fast drying (seconds or milliseconds) and relatively short exposure time to heat. The solid particles obtained present relatively narrow size distribution at the submicron-to-micron scale. Generally, the yield% of spray-drying at laboratory scale with conventional spray-dryers is not optimal (20–70%) due to the loss of product in the walls of the drying chamber and the low capacity of the cyclone to separate fine particles (<2 μm). Aiming to overcome this crucial drawback in early development stages, new devices that enable the production of submicron particles with high yield, even for small sample amounts, have been introduced into the market. This review describes the most outstanding advantages and challenges of the spray-drying method for the production of pure drug particles and drug-loaded polymeric particles and discusses the potential of this technique and the more advanced equipment to pave the way toward reproducible and scalable processes that are critical to the bench-to-bedside translation of innovative pharmaceutical products.

Contents

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1. Introduction: The spray-drying technique

Spray-drying is a technique based on the transformation of a fluid into a dry powder by atomization in a hot drying gas stream that is generally air [1]. The spray-drying process consists of four fundamental steps: (i) atomization of the liquid feed, (ii) drying of spray into drying gas, (iii) formation of dry particles and (iv) separation and collection of the dry product from the drying gas [2–4]. Fig. 1 shows a scheme of the conventional spray-drying process. First, the fluid is fed into the drying chamber by a peristaltic pump through an atomizer or nozzle that can be a rotary atomizer, a pressure nozzle or a two-fluid nozzle and the atomization occurs by centrifugal, pressure or kinetic energy, respectively [5]. The small droplets generated (micrometer scale) are subjected to fast solvent evaporation [6,7] leading to the formation of dry particles that are separated from the drying gas by means of a cyclone that deposes them in a glass collector situated in the bottom of the device [8,9]. Heng et al. described in detail the major phases involved in spray-drying process [10]. In addition, a description of the emergence and evolution of this technology and the hardware used in the process is available in the literature [11]. The fluid feeds in spray-drying can be solutions, suspensions, emulsions, slurries, pastes or melts [12–14]. Solid products obtained after the process have the advantage of higher chemical and physical stability compared to liquid formulations. In addition, they can be used as precursors for the production of other suitable dosage forms such as capsules or tablets [15–17].

The operation configurations in spray-drying can be *open-loop* or *closed-loop*. The former uses air as drying gas that is not re-circulated, while the latter an inert gas (e.g., nitrogen) that is re-cycled in the drying chamber throughout the entire process. The *open-loop* configuration is usually preferred in most of the cases since it is more cost-effective and stable [18,19]. However, the *closed-loop* mode is used to prevent the mixing of explosive gases [4] and for the manipulation of substances that are sensitive to oxygen [20].

Regarding the direction of the drying gas flow with respect to the direction of the liquid atomization, there exist two possibilities, co-current flow (same direction) and counter-current flow (opposite direction) (Fig. 2). In the first case, the final product is in contact with the coolest air, hence is preferable for the drying of heat-sensitive materials [2]. In the second case, the dry product is in contact with the hottest air and therefore it cannot be used with temperature-sensitive materials, but is desirable in terms of higher thermal efficiency. In addition, there are intermediate configurations with mixed flow between co-current and counter-current [20,21].

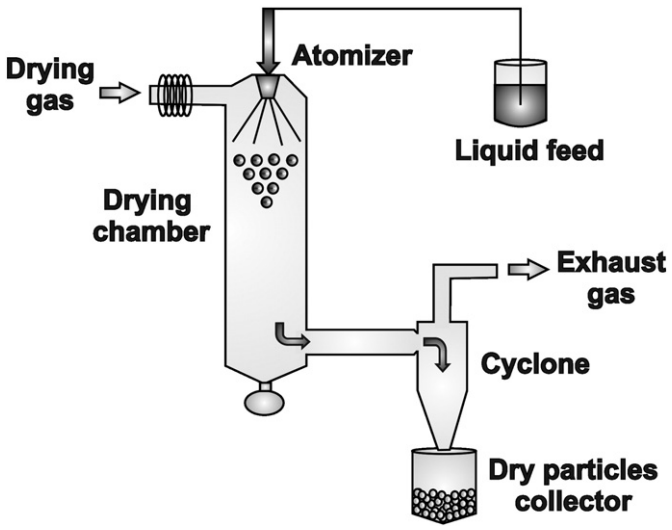

Fig. 1. Diagram of the equipment and process of conventional spray-drying.

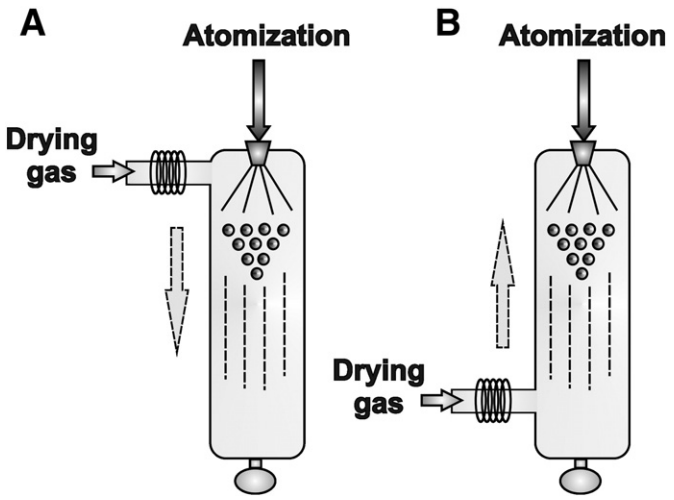

Fig. 2. Scheme of (A) co-current flow and (B) counter-current flow. The full lines represent liquid atomization and the dashed lines represent drying gas.

The variables that affect the characteristics of the product and that can be tuned are (i) process parameters, (ii) properties of the liquid feed and (iii) equipment design (Table 1) [6,9,22–26]. For example, high flow rate of the liquid feed, large nozzle diameter and high formulation concentration favor the formation of larger particles. Conversely, low surface tension, high atomization pressure and small nozzle diameter render smaller particles. Regarding the particles morphology, faster solvent evaporation rate (lower point boiling) usually leads to particles that are more porous due to shorter time for the droplets shrinkage [21,27–29]. Finally, the air outlet temperature is dependent on other process variables [9,24]. Nandiyanto and Okuyama reviewed in detail the particle design (i.e. control of size and morphology) during the spray-drying process to suit specific applications [30].

2. Main advantages of the spray-drying process

Spray-drying is a technique widely used in the pharmaceutical, chemical, materials, cosmetic and food industries [3,31,32]. The first patent concerning this technology was in the early 1870s. Thereafter, spray-drying underwent a constant development and evolution [11]. Patel et al. recently reviewed the patents employing spray-drying in the pharmaceutical, the food and the flavor industry [33]. In general, this technique is very appealing both under laboratory and industrial setups because it is rapid, continuous, reproducible, single-step, and thus, scalable without major modifications [1,28,34]. In this context, the final drying step required in other common techniques used to produce particles (e.g., emulsion/solvent evaporation) is not required in spray-drying [35–37]. Moreover, a successful bench-to-bedside translation greatly depends on the fulfillment of two conditions: scalability and

Table 1
Main adjustable parameters of the spray-drying technique.

Parameter		
Process	Liquid feed	Equipment
Flow rate of liquid feed	Concentration	Co-current flow
Flow rate of drying gas	Viscosity	Counter-current flow
Gas inlet temperature	Density	Mixed flow
Drying rate	Surface tension	Atomizer geometry
% aspiration	Solvent point boiling	
Pressure		
Type of gas		