REVIEWS

The Challenge of Drying Method Selection for Protein Pharmaceuticals: Product Quality Implications

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Received 7 July 2006; revised 29 October 2006; accepted 31 October 2006

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20842

ABSTRACT: Numerous drying methods are used to dry solutions of proteins in the laboratory and/or in pharmaceutical manufacturing. In this review article, we will discuss many of these drying methods. We will briefly introduce and compare the unit operations involved in the drying methods to give an insight on thermal history, and the different stresses that a drying method can present to an active ingredient, particularly for protein molecules. We will review and compare some important physico-chemical properties of the dried powder that result from using different drying methods such as specific surface area, molecular dynamics, secondary structure (for protein molecules), and composition heterogeneity. We will discuss some factors that might lead to differences in the physico-chemical properties of different powders of the same formulation prepared by different techniques. We will examine through a literature review how differences in some of these properties can affect storage stability. Also, we will review process modifications of the basic drying methods and how these modifications might impact physico-chemical properties, in-process stability and/or storage stability of the dried powders. J Pharm Sci 96:1886–1916, 2007

Keywords: atomization; electron spectroscopy for chemical analysis; evaporation; freeze drying; glass dynamics; molecular mobility; protein stabilization; spray drying; spray freeze drying; surface analysis; vacuum drying

INTRODUCTION

Whether processing conditions during drying are altered or different drying methods are used to prepare the same formulation, the net result is modification of the thermal history. In polymer science, the effects of thermal history and drying method have been shown to influence relaxation time, diffusivity, stability, and glass transition temperature.[1] In the food industry, different drying methods commonly used in the pharmaceutical industry have been shown to affect product quality. For example, spray drying and freeze drying produced ovalbumin powders with different emulsification and foaming properties upon reconstitution.[2] Freeze drying caused greater losses in volatile ingredients in Petroselinum crispum than traditional oven drying and 'shade' drying, even at ambient temperatures.[3] Vacuum oven drying produced dried pectin powder of much lower solubility over a pH range of 2–10 as compared to freeze drying and spray drying.[4] Other issues such as color loss,[5] flow

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Journal of Pharmaceutical Sciences, Vol. 96, 1886–1916 (2007)

properties,[6] and preservation of labile ingredients such as vitamin C[5,7] and β-carotene[7] have also been a function of the drying method.

Spray drying and freeze drying are by far the two most popular methods of drying protein solutions in the pharmaceutical industry. Supercritical fluid technology, spray freeze drying (SFD), spray coating, and modifications of spray coating such as drying with conventional spouted bed,[8] and other drying methods based on solvent evaporation without atomization (such as vacuum drying, Xerovac®, foam drying, film drying) are also used but on a much smaller (mostly research) scale.[9–15] A few studies have been published in the pharmaceutical field that compare the effects of different drying methods on product properties. We will review some of this published work. It is important to investigate the effect of drying method and processing conditions on pharmaceutical properties of amorphous formulations. One can expect differences in the physico-chemical properties among powders of the same formulation dried by different methods, and even differences between their storage stability profiles have been documented.[16–18] In the pharmaceutical industry, drying is employed if the storage stability of the active ingredient (physical and/or chemical) in solution is unsatisfactory. The choice of drying method will then be associated mainly with the economics of drying and the intended route of administration. For example, spray-dried powders are commonly prepared when the intended route of administration is via inhalation, since the desired control over particle size can be obtained, but freeze drying is commonly employed for injectable products since sterility and "particle-free" quality attributes are more easily obtained in freeze drying. Improving storage stability is often focused on re-formulation, which in many times can be tedious and time consuming, but variations in processing specifics can also address stability issues. However, a full understanding and appreciation of the stresses encountered during drying, and secondly the influence of the drying method (or thermal history) on the physico-chemical properties of the dried formulations is needed to choose the appropriate drying process and to optimize this process for maximum product quality.

UNIT OPERATIONS, PROCESS VARIABLES, AND THERMAL HISTORIES INVOLVED IN DIFFERENT DRYING METHODS

Most drying methods involve removal of solvent by sublimation, evaporation or a combination of both. In this review, we classify the drying methods according to the main mechanism of solvent removal.

Drying by Evaporation

Spray Drying

Spray drying is a one-step economic drying method widely used to produce powders for pulmonary delivery.[19–21] The unit operations involved in spray drying are summarized in Figure 1. Briefly, the drying method in a spray dryer involves feeding the solution through an atomizer nozzle placed inside the drying chamber at a controlled rate. As the liquid stream emerges from the nozzle orifice, large liquid–air interfacial expansion will occur and the stream breaks up into small fine droplets (atomization) in the drying chamber by the aid of an atomizing gas (air or inert gas such as nitrogen). Viscosity, surface tension, and density of the liquid, as well as atomizing gas flow rate and pressure, influence the break up of the liquid and hence droplet size distribution.[22] Depending on the design of the atomizer nozzle, the liquid stream will mix with the atomizing gas right before or right after it emerges out of the nozzle orifice into the drying chamber. Other methods of atomization that have

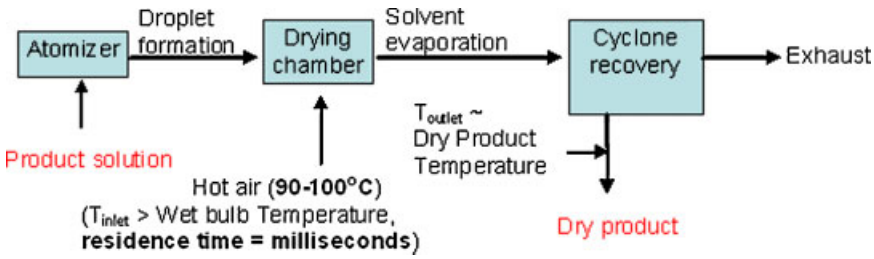

Figure 1. Unit operations involved in spray drying.