Chemical Engineering Science 172 (2017) 731–743

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

A freeze-drying microscopy study of the kinetics of sublimation in a model lactose system

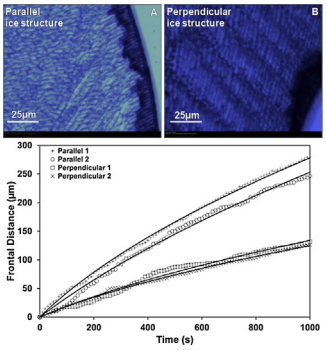
Purnima Ray (née Raman), Chris D. Rielly, Andrew G.F. Stapley *

Department of Chemical Engineering, Loughborough University, Loughborough, Leicestershire LE11 3TU, United Kingdom

HIGHLIGHTS

- Sublimation fronts were tracked using image analysis.
- Silver iodide was added as a nucleating agent to improve experimental reproducibility.
- Microstructure orientation shown to significantly affect sublimation front velocities.
- A surface mass transfer resistance is evident.
- The use of a vapour pressure driving force may be an oversimplification.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 6 December 2016
Received in revised form 13 April 2017
Accepted 26 May 2017
Available online 29 May 2017

Keywords:
Lyophilisation
Modelling
Mass transfer
Nucleation
Collapse temperature
Silver iodide

ABSTRACT

Freeze drying microscopy has been used to probe the lyophilisation kinetics of lactose solutions of various concentrations, at temperatures ranging from −50 °C to −30 °C and under a constant pressure of 1 Pa. Sublimation front velocities were determined by recording a sequence of video images of the sublimation and analysing the frontal progression using MATLAB. Initial experiments showed poor reproducibility. To combat this, silver iodide (AgI) was added as an ice nucleator, which raised nucleation temperatures and improved reproducibility when compared to non-AgI experiments. The lower supercooling on nucleation when AgI was used also produced larger ice crystals, which enabled the crystal microstructure of the more dilute samples to be more clearly observed. This showed long thin crystals, and the orientation of these crystals with respect to the direction of the frontal movement strongly affected frontal progression rates, which explained the earlier reproducibility problems. A twin resistance mass transfer model, comprising a fixed edge resistance and a resistance which increased with frontal depth, was able to describe the sublimation kinetics. The edge resistance first increased and then decreased with solids content. The resistance per unit depth increased exponentially with solids content, so much so that there is an optimal solids content in relation to the rate of production of dried material. Resistances were also much higher when crystals were oriented with their major axis perpendicular to the direction of frontal movement. Freeze drying rates were approximately proportional to the saturation vapour pressure of water, however the long-held belief that water vapour pressure is the main driving force for mass transfer in freeze-drying systems may be an oversimplification as this only reflects driving forces in the vapour phase (pores) rather than within the solid.

* Corresponding author.
E-mail address: A.G.F.Stapley@lboro.ac.uk (A.G.F. Stapley).

http://dx.doi.org/10.1016/j.ces.2017.05.047
0009-2509/

1. Introduction

Freeze-drying is a commonly-used technique in the pharmaceutical and food industries for increasing the shelf life and preserving the stability of labile products. Pharmaceutical applications include the freeze-drying of living cells, vaccines, enzymes, and biological media. In the food industry, freeze-drying is applied to the manufacture of products such as coffee, milk powder and infant formula (Chow et al., 2008; Fonseca et al., 2004; Nasirpour et al., 2007; Pardo et al., 2002; Thomas et al., 2004; Yang et al., 2010). The process involves freezing the desired product solution, followed by sublimation and secondary drying (Oetjen, 1999). Sublimation is the primary drying stage of the freeze-drying process, where removal of ice as water vapour takes place at very low temperatures. Secondary drying then follows, where the water is further desorbed from the freeze concentrated solid. As a low temperature process, freeze-drying has the advantage of causing reduced damage compared to higher temperature methods such as spray drying. However it has the disadvantages of being a time and energy intensive process (Tang and Pikal, 2004).

The main steps in a freeze-drying process are the freezing and sublimation steps, which can indirectly and directly influence the cycle duration (Meister et al., 2009). Improvements to the freezing process are often focussed on reducing refrigeration costs. However, the freezing step also determines the internal structure of the frozen material. In particular the rate of freezing influences the size of dendritic and cellular ice crystals. A highly porous structure with reduced diffusional resistance will improve mass and heat transfer during sublimation, thereby reducing the primary drying cycle duration and increasing the overall process efficiency.

Many different methods and devices have been developed over the years to study and improve low temperature freezing and freeze-drying processes (Rosenthal and Rall, 1984; Nail et al., 1994). One such development is freeze-drying microscopy (FDM), which allows the direct visualisation of the sublimation front, as the dried region appears much darker than the undried icy region (Pikal et al., 1983). Light is transmitted through the icy region with minimal scatter, as the two phases (ice and the freeze concentrated matrix) have similar refractive indices. However, when the ice sublimes to leave voids, the large difference in refractive index between the air pores and the solid matrix causes significant scatter. Thus, the boundary between the two regions is obvious. Ice sublimation only occurs at the front as the microscope slide is firmly sealed to the sample when the (liquid) sample is frozen, and so there is no headspace for the icy region to sublime into other than via the edge of the slide.

The most common current use of FDM is the determination of collapse temperatures (T_c) of products to be freeze-dried. Here, the temperature is allowed to rise as freeze drying progresses. The collapse temperature is defined as the temperature above which loss of structure (or shrinkage) of the product occurs, and is of great importance to an industrial production process as it defines the highest temperature to which the undried frozen product can be exposed without adversely affecting the freeze drying, rehydration properties and storage stability of the sample. Since an increase in temperature can directly increase the productivity by reducing the sublimation time, it can safely be said that T_c is of critical importance to the sublimation process (Pikal and Shah, 1990). Product collapse occurs as a consequence of a transition of the solute phase from the glassy into the rubbery state near the ice-vapour interface, resulting in a decrease in the viscosity of the solute phase and a loss of the porous structure created during the sublimation of ice (Pikal and Shah, 1990).

The freeze-drying microscope allows visualisation of collapse, as the collapsed region is able to transmit light with minimal scatter due to the absence of pores. If the temperature of a freeze drying sample is gradually increased, then a transition from "dark" to "light" will be observed just behind the front as the sample moves through the collapse temperature.

There are many reports in the literature regarding the use of FDM to determine the T_c of various products, for which it is now a well-established technique (Adams and Ramsay, 1996; Meister and Gieseler, 2009; Meister et al., 2009; Yang et al., 2010; Zhai et al., 2003). However, very few researchers have used FDM to determine frontal velocities or to link them to sublimation rates. This can, in part, be attributed to the time-consuming nature of the analysis, particularly before computational image analysis techniques have become available. For example, Pikal et al. (1983) used FDM to study the morphology of the crystal/pore structure produced from different freezing and annealing regimes, but still preferred to use a microbalance technique rather than FDM to study freeze drying kinetics. The first reported use of FDM to determine kinetics appears to be by Kochs et al. (1989, 1991), who developed a FDM device which allowed a temperature gradient to be produced across the sample in the initial freezing stage. This resulted in nucleation at one end of the sample and subsequent directional solidification across the sample. Very regularly spaced columnar crystals were produced and the kinetics of the subsequent freeze drying phase could be related to the width of the columnar crystals. Zhai et al. (2003) used a commercially available FDM device to study freeze drying kinetics various materials including buffer solutions, a suspension or glass beads and pure ice. The frontal distances varied with the square root of time, and was fitted to a diffusion model (flux proportional to concentration gradient or pressure gradient through the dry layer). The authors characterised the systems in terms of an effective diffusion coefficient through the dry layer. Sublimation times calculated using these D_{eff} values were in broad agreement with the sublimation times in a conventional laboratory vial freeze-dryer for the glass bead system but not for the buffer solutions. This was attributed to cracks appearing in the samples in the vials. It is well known however that the rate of freeze drying is heavily dependent on the microstructure produced by the freezing process, which may be very different between that produced in a vial and that on a microscope slide (Kochs et al., 1989).

The purpose of the current study is to further explore and develop the FDM technique for gaining velocity data of the sublimation front, and in particular how they relate to the porous microstructure. Although very different to conventional systems, this should allow insights to be gained more generally into freeze drying processes and help understand conventional systems better.

2. Materials and methods

2.1. Materials

α-Lactose monohydrate (99.5%), sodium chloride (99.5%), magnesium chloride (>98%), potassium chloride (99%) and silver iodide (AgI, 99%) were purchased from Fisher Scientific/Acros Organics (Loughborough, UK). Sodium chloride, magnesium chloride and potassium chloride were used as eutectic mixtures for the temperature calibration of the microscope stage. Lactose was stored in an air-tight bottle to prevent moisture absorption.

2.2. Determination of moisture content

The Karl Fischer titration method was used to determine the moisture content of the as-received α-lactose monohydrate (Schuck and Dolivet, 2002). The oven drying or high temperature