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Using Texture Analysis Technique to Assess the Freeze-Dried Cakes in Vials

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ABSTRACT

A freeze-dried (FD) cake should possess, among other properties, a sufficient dryness and strength to prevent cracking or powdering during transportation and storage. In this study, the application of a standard texture analysis (TA) technique to study the mechanical properties of the FD cakes directly in glass vials used for freeze-drying has been demonstrated. Examining the FD cakes in glass vials has many advantages as it allows studying the intact FD cakes minimizing the bias from texture distortion during samples preparation, and reducing the moisture uptake. A procedure allowing quantitative assessment of the strength, fracturability, and elastic properties of the FD cakes using TA has been developed. The results show that the TA method is sensitive to the variations in cake materials, storage conditions (temperature, excessive moisture), and cake quality. The results also show that TA can also be applied for optimization and improvement of the freeze-drying protocols and rapid disintegrating tablet formulation development. The simplicity of the TA technique and a number of different probes available on the market allow using the TA for the routine reliable and robust tests of FD solids providing valuable information on the strength and texture of the cakes.

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Introduction

Freeze-drying, or lyophilization, is a standard commonly used method for the production of long-term stable solid products. Principles and applications of freeze-drying in the pharmaceutical and biotechnology industries were widely described in many books and review papers.[1-3] The most frequently used containers for freeze-drying are glass vials and blister packs. Freeze-dried (FD) products in vials are usually stoppered at the end of the freeze-drying run under controlled atmospheric conditions (vacuum or inert gas).[3,4]

To be considered acceptable, an FD cake (or plug) should occupy the same volume in a vial as the original frozen mass and possess, among others, the following quality attributes: (1) sufficient dryness, (2) uniform color and consistency, and (3) ability to be rapidly reconstituted upon addition of liquid.[1-3,5] In addition, some applications (for instance, production of the orally disintegrating tablets by lyophilization) also required FD cakes to be of a sufficient strength to prevent cracking or powdering during transportation and storage to meet the patient compliance. The desired qualities can be achieved due to both the proper product formulation and freeze-drying cycle optimization.

There are many different experimental methods for evaluation of the FD cakes; some of them are summarized by Devi and Williams.[6] According to these authors, the most widely used analytical methods to characterize the quality of the FD cakes are scanning electron microscopy (SEM), freeze-drying microscopy, differential scanning calorimetry (DSC), X-ray powder diffraction, and Karl Fisher, which examine the internal structure of the cakes, crystalline and amorphous state, and the residual moisture, respectively. Besides, different novel experimental techniques and approaches are being developed to characterize the cake appearance and the frozen structure of pharmaceutical formulations (for instance, the direct optical microscopy method in cold chamber[7] and measurement of shrinkage and cracking using imaging of the lyophilized cakes[8]). In contrast, the mechanical properties of the FD cakes (unlike the mechanical properties of non-FD solid dosage forms) are rarely assessed. At the same time, the mechanical properties can provide valuable information on the strength and susceptibility to breakage of the FD cakes as well

Abbreviations used: DSC, differential scanning calorimetry; FD, freeze-dried; PVP, polyvinylpyrrolidone; RDTs, rapid disintegrating tablets; RH, relative humidity; SEM, scanning electron microscopy; TA, texture analysis.

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as on the quality of the lyophilization process. Besides, analysis of the mechanical properties and the texture of the FD cakes can help improve the freeze-drying protocols as the properties of FD cakes (in particular, the pore size and wall thickness of FD solids) depend on the FD cycle parameters (i.e., temperature, pressure, rate).[9]

Texture analysis (TA) method is being widely used for product characterization in food, cosmetic, and pharmaceutical industries. For instance, TA application in cosmetic science has been described in the book by Barel et al.[10]; Tai et al.[11] consider an application of TA to quantify the texture properties of raw cosmetic and pharmaceutical materials; review papers by Tunick[12] and Chen and Opara[13] summarize the approaches, which are being used to measure the textures of food products. In the pharmaceutical industry, compressive mechanics has been widely used to study solid pharmaceuticals. However, while the vast majority of studies deal with examination of solid dosage forms, films, hydrogels, and so on, the mechanical analysis has been applied to assess the FD cakes only in a few works. Among these studies some authors produced and examined the tray-dried cakes cut into cubes[9] or Petri dish–dried gelatin matrices,[14] and some used a specific apparatus.[6,15]

The aim of this study was to develop and optimize a TA technique to study the compressive mechanical properties of FD cakes directly in glass vials using a standard commercially available texture analyzer. We also aimed to show a correlation between the texture profiles and the physical structure of FD cakes. In a typical experiment, a probe (in our case, a stainless steel cylindrical probe, 6 mm in diameter) is compressed into the central zone of an FD cake (Fig. 1a) and the force required to penetrate into a sample to a given distance (or % strain) is recorded against the displacement (or time). As the probe area is smaller than the cake surface, probe can puncture and break the FD cake; therefore, the approach described in this study can be called as a probe penetration test.

The downside of many experimental techniques exploited to analyze the structure of FD cakes (first of all, SEM) is a necessity to disturb or destroy the cake in order to prepare a sample for the analysis. In this case, the way of sample preparation might interfere with the experimental outcome. Moreover, it is known that many excipients are hygroscopic, especially in the FD state, and even brief contact with the moist room atmosphere can alter the cake texture. Examining the FD cakes directly in vials helps to avoid extra manipulations with cakes (cutting, transferring, etc.) thus minimizing the distortion of a sample, as well as the moisture absorption by a lyophilized product. Furthermore, this approach allows studying the internal layers across the initially intact FD cake. The latter advantage of the approach proposed in this study can be especially useful when developing and optimizing freeze-drying protocols and assessing the effect of the residual moisture on the cake texture.

As an illustration of the TA methodical approach proposed, its application for the development of the robust formulations of the rapid disintegrating tablets (RDTs) will be shown. Rapid (or orally) disintegrating tablets represent a pharmaceutical product for which the mechanical properties of the final dosage are among the critical quality attributes. The initial stages of the RDT formulation development often include lab-scale production of lyophilized cakes in vials. The analysis of the lyophilized products directly in the FD vials can provide a valuable, yet simply obtain, information on both the tablet mechanical strength and the texture features (i.e., fragility, elasticity).

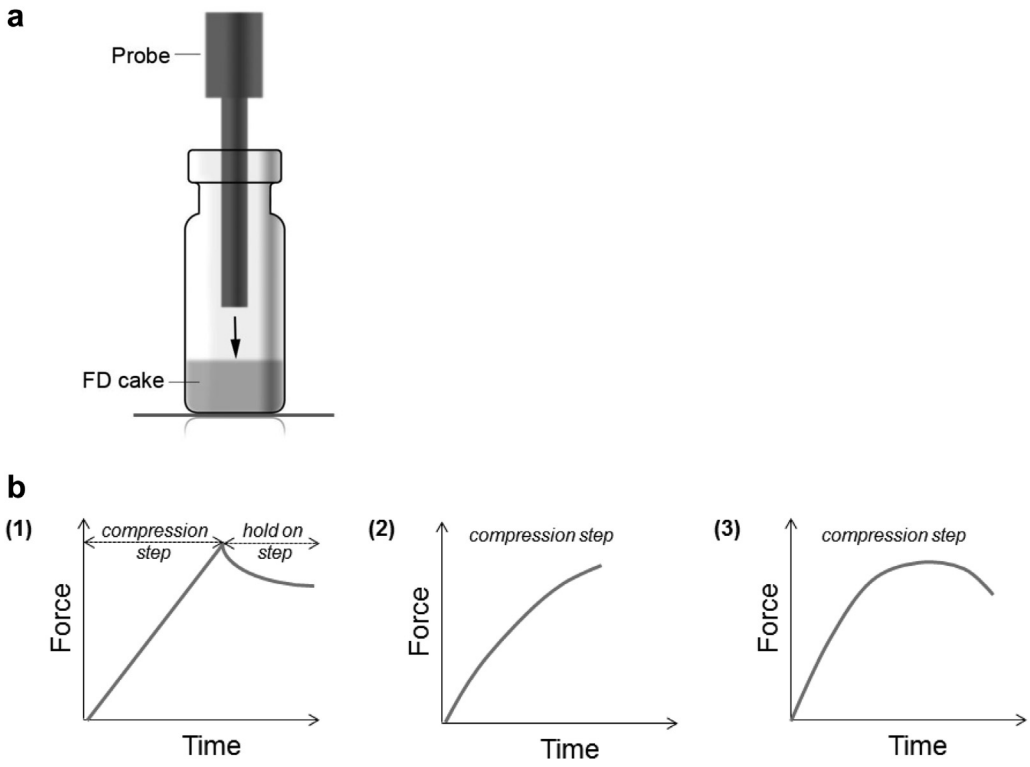

Figure 1. (a) General experimental setup. A cylindrical TA probe penetrates a FD cake to a given distance (or % strain). (b) Schematic "stress-time" curves illustrating a change in stress during compression (probe movement) and hold on (steady probe at a constant strain, shown only for curve 1) stages for (1) linear elastic deformation; (2) nonlinear elastic deformation; and (3) elastic-plastic deformation.

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