Micromechanical Thermal Analysis for Pharmaceutical Formulations

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Purpose

Common thermal analysis techniques such as Differential Scanning Calorimetry (DSC), Thermomechanical Analysis (TMA) or Dynamic Mechanical Analysis (DMA) are widely used to study the properties of pharmaceuticals as they change with temperature [1]. However, certain drawbacks are associated with these techniques such as large sample size (DMA, TMA), the lack of sensitivity for secondary relaxations (DSC) or long run times (all). Here, we present a thermal technique using resonating low stress silicon nitride (SixNy) microstrings to overcome the above-mentioned issues and create novel insights into the thermal and mechanical properties of pharmaceutical formulations.

Introduction

The measuring principle is based on the string's change of frequency during the temperature sweeps. As the silicon frame expands more than the SiN string during heating [2], the string's tensile stress increases, leading to higher resonance frequencies (see Figure 1). Thermal transitions of samples coated onto the string (see Figure 2) affect the tensile stress and result in frequency slope changes.

Materials and Methods

SiN microstring sensors are cleanroom fabricated by depositing (LPCVD) SiN on a silicon wafer, followed by patterning using standard UV lithography and dry etching steps as well as a KOH etch for device release. The sensors are placed on a custom build temperature stage inside a vacuum chamber to eliminate air damping of the mirco resonators and thus reduce measurement noise. The change in frequency is measured with a laser-Doppler vibrometer (MSA-500, Polytec GmbH, Germany). A setup overview is given in Figure 3.

Results

The current setup could successfully be utilized to analyze both small molecule (e.g. drugs) and large molecule samples (polymer, proteins). As an example, Figure 4 on the right hand side shows the thermal response of amorphous carvedilol coated onto a microstring. The inlet displays the reference measurement of the same uncoated string. A major change in slope of the relative frequency shift at 50 °C, representing the glass transition, is observed. The sample mass is approximated to be below 1ng.

[1] Qi S. (2016) Thermal Analysis of Pharmaceuticals. In: Müllertz A., Perrie Y., Rades T. (eds) Analytical Techniques in the Pharmaceutical Sciences. Advances in Delivery Science and Technology. Springer, New York, NY
[2] Bose, S., et al., Micromechanical String Resonators: Analytical Tool for Thermal Characterization of Polymers. ACS Macro Letters, 2014. 3(1): p. 55-58.

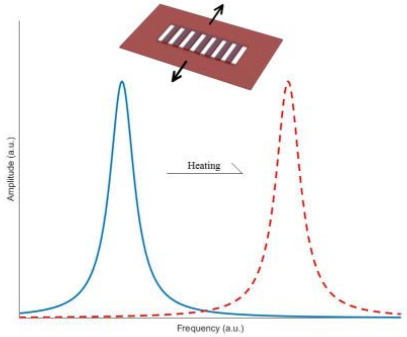

Figure 1. Measuring principle

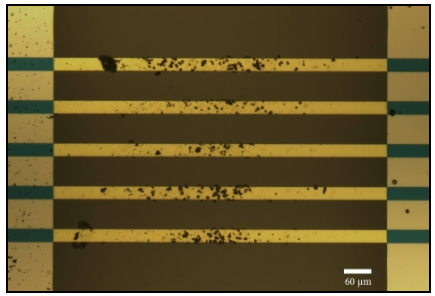

Figure 2. Light microscope picture of a coated string sensor

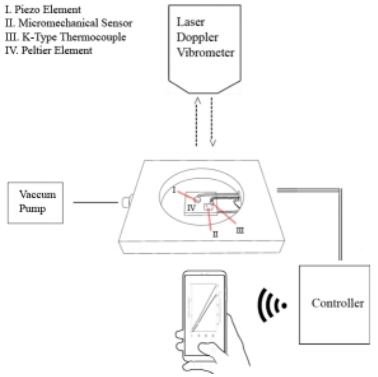

Figure 3. Instrumental setup overview

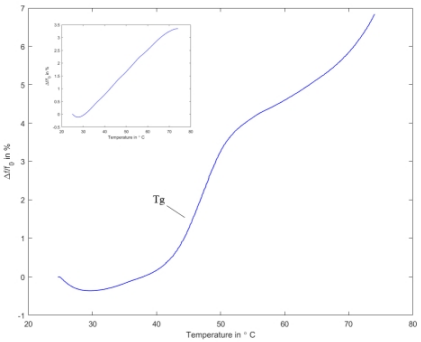

Figure 4. Glass transition of amorphous carvedilol