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Fully-automated ultrasensitive DSC for high-throughput studies of biopharmaceutical formulations and drug discovery

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Ultrasensitive DSC is commonly used to characterize the structure and stability of proteins and other biopolymers down to concentrations of 0.1 mgm/ml and below. With existing instruments, sample throughput can be a limiting factor for certain applications. Three such applications are:

- Biopharmaceutical formulation stability studies, where a single protein biopharmaceutical is examined in a multitude of different solutions;
- Characterization of mutant protein stability where a vast number of protein variants might be examined in the same solution;
- Ligand binding studies, measuring the T_m of proteins in the absence and presence of a variety of ligands (i.e. potential drugs), and determination of relative binding constants.

A new DSC, the VP-Capillary DSC Platform, has been developed for applications requiring higher throughput. Two advances increase the throughput. First, the instrument scans effectively at rates up to 250 ºC/hr or about 3 times faster than conventional ultrasensitive DSCs. Second, the instrument is mated to a fully-integrated autosampler which allows for unattended operation; samples are placed in wells of conventional microtiter plates, VPViewer™ software controls all cell cleaning, cell filling, and scanning operations, and Origin® software is used for post-run data analysis. Maximum throughput is up to 50 samples during 24 hours of continuous, unattended operation, but the exact number will depend on the details of experiment parameters such as temperature range, scan rate, etc.

The sample and reference cells, formed from tantalum capillary, have small working volumes of ~130 microliters which permit rapid equilibration consistent with the fastest scan rates. Instrument response time is software-selectable (US patent 5,967,659 and others pending) to maximize performance at all scan rates. An improved adiabatic mode (US patent 5,813,763 and others pending) is used for upscanning over the temperature range –10 to +130 ºC, while downscanning is nonadiabatic. Experimental results will be discussed.