Monitoring secondary (solute+water) crystallization by DSC, synchrotron X-ray diffraction, and in vials using heat flux transducer

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ABSTRACT

Crystallization of excipients during freeze-drying could have a major impact on both the manufacturing process (e.g., rate of drying) and quality of the finished product. In this investigation, binary solutions of water+NaCl and water+surfactant (poloxamer) were studied by DSC, low-temperature synchrotron small- and wide-angle X-ray diffraction (XRD), and heat-flux transducers (HFT) which are incorporated into the shelf of a Millrock Technology, Inc. MicroFD freeze-dryer with LyoPAT II. In the HFT experiments, the heat flux between the shelf and vials was measured during cooling/warming cycles. For NaCl-water solutions, primary ice nucleation and secondary solute+water crystallization (equivalent to eutectic crystallization for a binary system) during cooling, and secondary (eutectic) solute+ice and ice melting during warming were detected by HFT. Behavior of poloxamer-water system was more complex, with at least three consecutive transitions taking place during cooling, i.e., primary water crystallization, formation of a liquid crystalline (tentatively, cubic) phase, and finally appearance of a crystalline poloxamer phase with 3-dimensional translational order. The study confirms that crystallization behavior as observed by laboratory-based tests (DSC and XRD) could be different from the behavior of a formulation during real freeze-drying runs, and also presents HFT as a useful non-invasive tool to monitor excipients crystallization in vials.

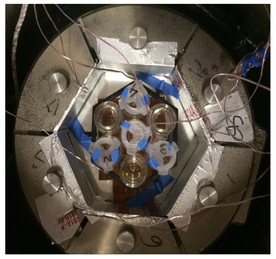
PURPOSE

Evaluate feasibility of using heat flux transducers to detect secondary solute+water crystallization during freeze-drying.

METHODS

Binary model solutions water+NaCl (5 and 15 wt% solute) and water+poloxamer (5 and 10 wt% solute) were filtered using 0.22 filter, filled into glass vials, and loaded into Millrock Technology, Inc. MicroFD freeze-dryer (photo below), on top of the HFT. Either one or seven vials were used in different tests; a photo of experimental set-up with 7 vials is given below. Product temperature was monitored by thermocouples during freeze/thaw cycles. Controlled ice nucleation was used in the HFT experiments. Total of 13 runs were performed.

Poloxamer-water solutions with poloxamer concentration 10 wt % were studied by both DSC and low-temperature synchrotron small- and wide-angle X-ray scattering (WAXS/SAXS), and with poloxamer concentration of 0.63 and 0.17 wt% by DSC. The SAXS/WAXS experiments were performed at the European Synchrotron Radiation Facility (ESRF), Grenoble, France.



RESULTS: DSC

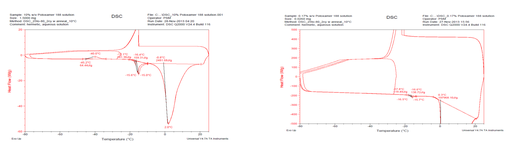


Fig 1. DSC cooling/heating curves of 10 wt% (left) and 0.17 wt% (right) poloxamer solutions. Solute+water crystallization observed during warming of 10 wt% solution between -45 and -35C. In 0.63 % (not shown) and 0.17 % solution, crystallization event was not detected either during cooling or warming.

RESULTS: sSAXS/WAXS

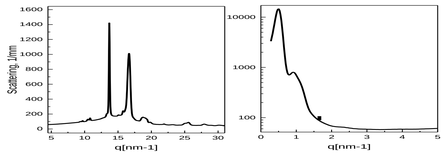


Fig 2a. SAXS (right) and WAXS (left) patterns of P188 obtained at room temperature. Ratio of the peak positions in the SAXS pattern is 1.82, close to the characteristic ratio of hexagonal phase of 1.73.

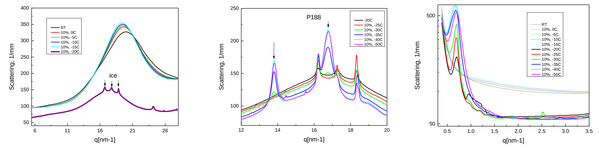


Fig 2b. Low-temperature synchrotron SAXS and WAXS of 10 wt% poloxamer solutions obtained during cooling. Ice formation was observed between -15 and -20C (WAXS patterns, left), whereas crystalline peaks of P188 (3-d structure) appeared at a lower temperature between -25 and -30C (WAXS patterns, center) center. Development of long-range structure was detected by SAXS in the same temperature range as ice formation, at -15 to -20C (right), i.e., before the formation of the 3-d structure. Note that pure “as is” P188 has hexagonal structure whereas the frozen solution corresponds to cubic structure..

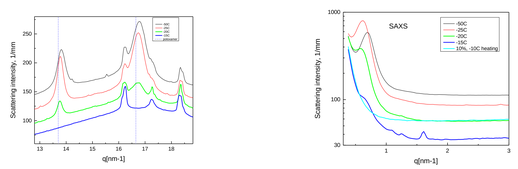


Fig 2c. Low-temperature synchrotron SAXS and WAXS of 10 wt% poloxamer solutions obtained during warming. The warming data shows that P188 melting proceeds in two steps, first disappearance of 3-d positional order (WAXS, center, -20 to -15C), and then long-range positional 2-d order (SAXS, -15 to -10C).

RESULTS: HFT (NaCl 15%)

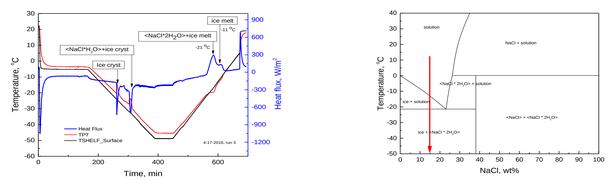


Fig 3. Temperature and HFT data for cooling/heating cycle of 15 % NaCl solution (left) and phase diagram of NaCl-water system (right). Cooling: both primary ice formation and secondary NaCl*2H2O+water crystallization were detected by HFT.
Warming: both eutectic melt and ice melt were detected by HFT. Transition temperatures by HFT during warming (Te = -21C and TL = -11C) are close to that from the phase diagram (Te = -21.4C and TL = -13.1C)

RESULTS: HFT (NaCl 5%)

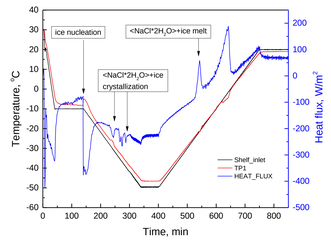


Fig 4. Temperature and HFT data for cooling/heating cycle of 5 % NaCl solution (7 vials). Both secondary crystallization during cooling and secondary melt during heating were detected by HFT, indicatively sufficient sensitivity. Multiple secondary crystallization events are detected, showing that controlled ice nucleation does not necessarily assure consistent secondary crystallization

RESULTS: HFT (P188, 10% and 5 %)

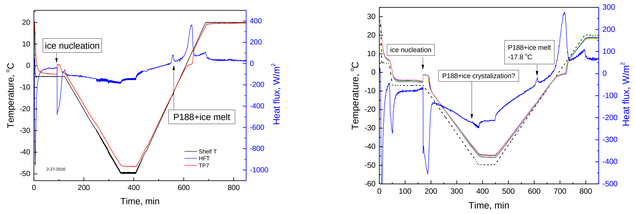


Fig. 5. Temperature and HFT data for cooling/heating cycle of 10 % (left) and 5% (right) P188 solutions. P188+ice melting during warming was detected in both cases, with temperature from HFT in agreement with DSC and XRD measurements. Secondary crystallization, however, was not detected by HFT

CONCLUSIONS

SAXS/WAXS: Crystallization/melting of P188 proceeds in two steps. During cooling, 2-d cubic structure forms followed by development of 3-d order, and the sequence of the transitions is reversed during warming, when the 3-d structure melts at lower temperature while 2-d cubic structure is still intact.
HFT: Secondary crystallization and melting was detected in NaCl-water solutions. Multiple secondary crystallization events are detected during cooling, demonstrating that controlled ice nucleation does not necessarily result in a consistent secondary crystallization. For P188-water system, while secondary melt is observed during warming, secondary crystallization is not detected even in the most concentrated solution. The behavior of P188-water system appears to be more complicated inside the vial and requires further investigation. Note also that, according to DSC, P188 crystallization was observed during warming of the frozen solution, whereas SAXS/WAXS detected crystallization of P188 during cooling.