# APPLICATION NOTE 161

# Specific Surface Area Measurement of Intact Lyophilized Cakes

## Introduction and Significance

As physical characterization of pharmaceuticals becomes more of a focus, analytical techniques must be able to provide data that is representative of the materials being analyzed. Companies are implementing. Quality by Design (QbD) and Process Analytical Technologies (PAT) initiatives to ensure robustness of formulas, processes, and products. Lyophilized products have key areas where these initiatives can play roles in product and process knowledge. Measurement of the surface area of lyophilized cakes provides valuable information on process capability and product consistency. BET surface area analysis of lyophilized products currently requires manipulation of the cake prior to testing to introduce the sample into the instrument sample tubes. This type of sample preparation technique for BET surface area testing may introduce error resulting in the lack of repeatability and robustness of the analysis and possible misrepresentation of the true surface area of the sample. Also, since manipulation is destructive to the sample, no further testing can be performed.

Possible variability stemming from non-standardized extraction techniques for removing cakes from their vials may lead to less reliable surface area data. We have developed a special prototype lyophilization vial holder apparatus that attaches to the Micromeritics ASAP 2420 Surface Area and Porosity Tester that will allow for non-destructive, intact lyophilized cake testing of surface area. In this preliminary study, we have found that surface area measurements of intact lyophilized cakes are approximately 35 – 55% less than the surface area of the same samples that have been manipulated during preparation. Further development of this product enhancement will lead to an invaluable characterization technique for lyophilized products during product development, scale-up, and as an implementable PAT tool for control of this critical process parameter.

## Lyophilization Method

Full chamber loads of model product in 20cc tubing vials were processed in a 48 square foot lyophilizer within a GMP aseptic environment. The product selected for the purposes of the preliminary BET testing was amorphous sucrose. Lyophilization cycles utilized either a standard freezing technique or employed a controlled nucleation methodology using rapid depressurization of the product chamber.

## Specific Surface Area Method of Analysis

In the present study we accept that temperature may be controlled by various methods and that commercial temperature controllers provide repeatable performance. Rather than studying temperature control, this document will evaluate the topic of vacuum versus flowing degas.

The vial is placed onto the sample holder and the sample holder/vial combination is then placed on the analysis port of the ASAP 2420 using a ferrule, frit and o-ring.

A step-wise manual evacuation is performed on each sample. The samples are left on the analysis port under evacuation with no added external heat for 16 hours to ensure any possible contaminants have been removed prior to beginning the test.

Sample analysis is started at liquid nitrogen temperatures with no backfill at the start of analysis. The sample is run using krypton over a ranges of relative pressures from 0.045-0.24 P/PO.

micromeritics®

## Results

Results are presented for 5 separate analyses. Specific Surface Area (SSA) is reported for samples of intact cakes, tested in their lyophilization vials and samples that have been manipulated (broken into pieces and removed from their vials and introduced into instrument-specific sample tubes.).

| SAMPLE | TYPE | SS ($M^2/G$) MANIPULATED CAKES | SS ($M^2/G$) INTACT CAKES | % DIFFERENCE |
|---|---|---|---|---|
| 1 | Sucrose | 0.8663 | 0.5481 | -36.7 |
| 2 | Sucrose | 0.8030 | 0.5167 | -35.7 |
| 3 | Sucrose | 0.4384 | 0.2060 | -53.0 |
| 4 | Sucrose | 0.3704 | 0.1868 | -49.6 |
| 5 | Sucrose | 0.8854 | 0.4609 | -47.9 |

## Conclusion

Data presented from this preliminary study show a significant difference in specific surface area of lyophilized cakes when the cakes are tested intact versus non-intact. This research demonstrates important and useful advances being made for surface area analysis for lyophilized samples. We are currently continuing to develop this technology through iterations of the sample vial holder and analysis conditions.

Once implemented, this technology will allow for a more convenient, direct, and efficient means of obtaining surface area measurements of intact lyophilized cakes while still allowing further physical characterization testing of intact cakes following surface area measurement.