TAM IV
ISOThERmal
MICROCALORIMETER

Modular
Ultra-Sensitive
High Throughput
TAM IV | MICROCALORIMETRY SYSTEM

It is completely modular and combines the highest heat flow sensitivity with unmatched long-term temperature stability to measure processes that are undetectable by other techniques. The TAM IV-48 expands the TAM IV capabilities as a high-throughput microcalorimeter system that can be configured to accommodate up to 48 individual calorimeters. The power and flexibility of the TAM IV thermostat, coupled with the available calorimeters and accessories, creates a flexible, powerful analytical platform suitable for any laboratory and offers performance and sample throughput that is unmatched by any other isothermal calorimetry instrument.

Features & Benefits:

TAM IV
- More responsive temperature control provides faster thermal equilibration and extended temperature range of 4 °C to 150 °C for real-world cold storage applications.
- Unmatched temperature stability for accurate heat flow measurement in experiments that last anywhere from a few hours to days and weeks.
- Four calorimeter positions that can be equipped with up to four calorimeters, each of which operates simultaneously and independently.
- Calorimeters are available in a wide variety of configurations: size, sensitivity, throughput, and ancillary sample measurement or manipulation capabilities.
- Accessory Interface box with capacity for up to eight separate accessories for unmatched flexibility.
- Advanced I/O module for interfacing up to three independent probes/sources, such as pH probe or light source.

TAM IV - 48:
- Easy configuration of 1 to 48 minicalorimeters for high throughput, parallel sample measurements for maximizing laboratory productivity.

TAM IV Micro XL:
- Specifically designed for battery testing with the new Micro XL Calorimeter and additional capacity for parallel measurements of 5 to 10 additional individual calorimeters.

Unique isothermal calorimetry platform for screening biologicals, energetic materials and production control testing.

The TAM IV is the world’s most SENSITIVE, STABLE AND FLEXIBLE microcalorimeter system.
The TAM IV calorimeter system efficiently and accurately controls the set temperature for the thermostat with advanced hardware and electronics. Precise temperature control and unmatched calorimeter sensitivity ensure all measurements being made will have the best stability, signal-to-noise ratio and reproducibility, even for the most challenging applications.

TAM IV Thermostat Features & Benefits:

- An oil based liquid bath system for a continuously circulated heat sink medium that prevents any thermal event in the room environment from altering the constant temperature bath or affecting any of the calorimeters
- A temperature regulation system utilizing state-of-the-art electronic thermistors and sensors to constantly adjust the heating, cooling and uniform oil flow speed for a temperature drift over 24 hours of less than ±0.01 °C
- The continuously circulated oil acts as a heat sink medium, and provides a uniform and precise temperature environment for sample testing when operating in isothermal, scanning or step isothermal modes.

Temperature Control Features & Benefits:

- Isothermal:
  - Classical mode for microcalorimetric measurements
  - Thermostat is maintained at constant temperature while heat generated or absorbed by the sample is measured
  - Both short term and long term experiments can be accurately performed with exceptional stability and reliability

- Step isothermal:
  - Perform multiple isothermal temperature analyses in a single experiment
  - Identical signal stability and sensitivity is achieved as in conventional isothermal experiments.
  - Data recorded continuously for detecting temperature-dependent events during step temperature changes, as well as in isothermal dwells

- Scanning:
  - Experiments performed under extremely slow and well controlled scanning conditions provides greater resolution of phase transitions compared to conventional DSC instruments
  - The slow scan rate (maximum 2 °C/h) allows large samples to be analyzed close to thermal, physical and chemical equilibrium
  - The slow scanning rate allows the possibility of verifying that a reaction follows the Arrhenius relationship.

<table>
<thead>
<tr>
<th>Heat Flow (mW)</th>
<th>Sample temperature (°C)</th>
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</thead>
<tbody>
<tr>
<td>-1.5</td>
<td>70</td>
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<tr>
<td>-1</td>
<td>71</td>
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<tr>
<td>-0.5</td>
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<tr>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>1.5</td>
<td>76</td>
</tr>
</tbody>
</table>
The TAM IV is designed for reliable operation at an extended temperature range of 4 °C to 150 °C. The expanded sub-ambient temperature range extends the application capability of the TAM IV to more accurately simulate low temperature conditions and accurately assess Arrhenius kinetics.

Features & Benefits:
- The TAM IV utilizes proven hardware and electronic controls to ensure stable and reliable operation from 4 °C to 150 °C
- User installable dry gas purge system ensures condensation free environment
- User programmable temperature settings for easily and accurately characterizing biological and ecological samples at sub-ambient environmental conditions
- Low temperature range is ideal for high precision sample analysis (food/freeze-dried pharmaceuticals, batteries) at representative cold storage/operation temperatures
- Enhanced data acquisition for stability and kinetics data below the glass transition point for samples with glass transition temperatures near ambient temperature
- Lower temperatures enable the accurate and reproducible characterization of samples exhibiting fast reaction rates with short induction times

The **BROADEST and most ACCURATE TEMPERATURE RANGE**
The primary TAM IV calorimeters are heat flow calorimeters. All calorimeters are twin type calorimeters, consisting of a sample and a reference and measuring the heat flow difference between the two positions. All installed calorimeters can operate simultaneously and independently.

**Calorimeters Feature & Benefits:**

- Enables experiment optimization based on
  - sample volume
  - absolute sensitivity
  - throughput
- Addition of external stimuli and complimentary measurements such as humidity, titration, electrical potential, atmospheric pressure, and more
- Maximum sensitivity with the Nanocalorimeter and Microcalorimeter featuring user-accessible reference positions
- Optimum sample throughput with Micocalorimeters utilizing a fixed reference to reduce the space occupied by the calorimeters

**Heat flow measurement**

The TAM IV heat flow calorimeters are designed to facilitate the transfer of the heat produced or consumed by any process in the sample through heat flow sensors. A thermoelectric sensor responds to a temperature difference by generating a potential over the sensor, according to the Seebeck effect.

**Measuring principle characteristics:**

- One side of the thermoelectric sensor is in contact with the sample and the other is maintained isothermal through contact with the TAM IV thermostat via the calorimeter heat sink.
- The potential is measured as a voltage signal and is proportional to the heat flow generated by the sample.
- A heat flow measurement is a passive measurement and ideal for slower reactions.
- Exceptional temperature stability of the TAM IV thermostat ensures that the measured heat flow values, even over long periods of time, are stable, accurate and repeatable.
- A sample with a nearly identical inert reference reduces baseline noise by eliminating the effect of any small thermostat fluctuations on the measured heat flow.
- The dynamic correction mode uses the time constants of the loaded calorimeter and automatically calculates the signal using the Tian equation to resemble the process taking place in the sample.
- Dynamic correction decreases the time constant 3.5 times and is recommended for rapid reactions, such as those seen in titration experiments.

**Absolute Sensitivity**

![Sample Size](image-url)
The Nanocalorimeter and Microcalorimeter employ a user accessible reference and deliver the maximum in heat flow sensitivity. Heat flow measurements on these calorimeters are easily optimized by matching each specific sample condition with an appropriate reference material. The Nanocalorimeter is designed for up to 5 mL samples. The Microcalorimeter will accommodate larger samples and/or provide a larger gas phase above the sample.

Nanocalorimeter Features & Benefits:
- Achieves highest sensitivity with inert substance in user accessible reference
- Maximum sample flexibility for all static ampoules up to 5 mL
- Compatible with 1 mL and 4 mL micro reaction systems for
  - Titration
  - Perfusion
  - RH Perfusion
- Compatible with the 4 mL vacuum/pressure ampoule for simultaneous collection of heat flow and pressure data
- Each calorimeter occupies only one of the four positions in the TAM IV thermostat

Microcalorimeter Features & Benefits:
- Designed for larger volume samples - accommodates 20 mL static ampoules in glass, stainless steel and Hastelloy
- Compatible with 20mL, micro reaction systems for
  - Titration
  - Perfusion
  - RH Perfusion
- Uniquely designed for the TAM microsolution ampoule applications
  - Dissolution of very small amounts of solids in various solvents
  - Dissolution of slowly soluble substances
  - Heat of dissolution and kinetics of dissolution
- Compatible with the 20 mL vacuum/pressure ampoule for simultaneous collection of heat flow and pressure data
- Each calorimeter occupies only one of the four positions in the TAM IV thermostat
Minicalorimeters have a permanent reference and are designed to reduce the space occupied in the thermostat to increase sample throughput. An assembly of up to six minicalorimeters is designated as a multicalorimeter which occupies only one of the four calorimeter positions in the TAM IV thermostat.

Minicalorimeter Features & Benefits:
- Space-saving over-under design delivers high throughput calorimetry by maximizing the number of calorimeters that can be used simultaneously
- Removable mounted reference inserts ensure reference is matched to selected ampoule and sample properties
- Heat sink design provides highest responsiveness to changes in the thermostat temperature – ideal choice for temperature scanning experiments
- Choice of 4 mL and 20 mL sample size for maximum sample flexibility
- Simultaneous heat flow and pressure measurements with vacuum/pressure ampoules
- Up to forty-eight 4 mL minicalorimeters for high throughput simultaneous and independent measurements in TAM IV-48

Multicalorimeter Features & Benefits:
- 4 mL multicalorimeter - six 4 mL minicalorimeters
- 20 mL multicalorimeter - three 20 mL minicalorimeters
- Multicalorimeter assembly occupying one thermostat position increases sample throughput by three- to six-fold
- Maximum throughput and experimental design flexibility:
  - Choice of identical or different reference inserts for each calorimeter
  - Use of 20 mL vacuum/pressure ampoules
The TAM IV Micro XL is a powerful tool for measuring the electrochemical reactions occurring inside of a battery cell. Characterizing reactions occurring in a battery cell is critical to developing novel battery technology to address battery shelf-life and stability studies, as well as electrolyte and additive development. Experiments can be conducted under passive storage conditions, or in conjunction with a battery cycler to evaluate battery charging and discharging dynamics. The TAM IV Micro XL is a real-time, non-destructive, and extremely sensitive measurement device for R&D and Quality Control.

**Micro XL Features & Benefits:**

- User accessible reference calorimeter - Optimal thermal balance and high signal to noise allowing investigation of the smallest reversible reactions in a wide range of battery geometries (pouch, cell phone, pacemaker and coin).
- Built in lead wire access - Seamless integration with an external battery cycler for charge/discharge dynamics.
- Modular Thermostat - TAM IV expanded capability for multi sample comparison

The TAM IV Microcalorimeter is a powerful tool for measuring the electrochemical reactions occurring inside of a battery cell. Characterizing reactions occurring in a battery cell is critical to developing novel battery technology to address battery shelf-life and stability studies, as well as electrolyte and additive development. Experiments can be conducted under passive storage conditions, or in conjunction with a battery cycler to evaluate battery charging and discharging dynamics. The TAM IV Microcalorimeter is a real-time, non-destructive, and extremely sensitive measurement device for R&D and Quality Control.

**Microcalorimeter Features & Benefits:**

- Accommodates large volume glass or stainless steel ampoules when large samples are required.
- Microwatt level absolute sensitivity for heterogeneous mixture samples.
- Sample-above-reference design minimizes required space; occupies one position in thermostat.
- User-accessible reference for easy heat capacity balance optimization.
- Battery fixture and sample holders are available for easy and accurate measurement of static discharge and charge-discharge.
- Application flexibility includes:
  - Evaluation of battery component compatibility
  - Soil & sediment remediation
  - Food stability analysis
  - Whole living organism metabolism

The Macrocalorimeter is a large volume calorimeter designed for accurate heat flow measurements of samples requiring volumes up to 125 mL.

**Macrocalorimeter Features & Benefits:**

- Accommodates large volume glass or stainless steel ampoules when large samples are required.
- Microwatt level absolute sensitivity for heterogeneous mixture samples.
- Sample-above-reference design minimizes required space; occupies one position in thermostat.
- User-accessible reference for easy heat capacity balance optimization.
- Battery fixture and sample holders are available for easy and accurate measurement of static discharge and charge-discharge.
- Application flexibility includes:
  - Evaluation of battery component compatibility
  - Soil & sediment remediation
  - Food stability analysis
  - Whole living organism metabolism
The Precision Solution Calorimeter (SolCal) makes high precision measurements of heat generated or consumed during solid or liquid dissolution processes.

SolCal Features & Benefits:

- Semi-adiabatic (isoperibol) calorimeter for heat of dissolution measurements with high accuracy and precision
- Quantification of amorphous content in materials
- Discrimination of crystalline forms for polymorphism assessment
- Optimised for rapid dissolution reactions that are complete within 30 minutes
- Two available reaction vessel volumes (25 mL or 100 mL) for maximum application flexibility
- Operating temperature range of 15 °C to 80 °C ensures wide range of applications
- Application flexibility includes a SolCal configuration with titration capabilities
- Occupies one position in the thermostat

Static sample handling ampoules provide an appropriate environment for many types of samples and are critical to a well-designed calorimetric experiment. Static ampoules, also referred to as closed or sealed ampoules, contain the sample with no manipulation during the measurement.

Static Ampoules Features & Benefits:

- Static isothermal measurements are non-destructive and non-invasive to enable accurate post-calorimetric analysis
- Sealed disposable ampoules ideal for high throughput, routine measurements
- Range of ampoules provide flexibility and choice based on expected experimental conditions
- Chemical interactions and/or pressure development
- Choice of disposable or reusable ampoules
- Available volumes: 1, 3, 5, 20 and 125 mL
- Ampoule composition: glass, stainless steel and Hastelloy
- Sealing techniques: crimp seal, heat seal, screw cap and circlip cap
- Sealed with microhygrostat for user defined relative humidity
- Static ampoule applications include:
  - Stability, compatibility and safety assessment
  - Monitoring reaction kinetics and curing
  - Assessing polymorph stability and amorphicity
  - Detection of microorganism growth.
The micro reaction system (mrs) consists of open ampoules and accessories, such as syringe pumps or mass flow controllers, allowing for the direct manipulation or modification of the sample or its environment during the experiment.

**Micro Reaction System Features & Benefits:**
- Open ampoules allow for the widest range of sample manipulations
- Controlled addition and mixing for titration experiments and studying dissolution characteristics
- Perfusion of gas or liquid over sample for absorption/adsorption studies
- RH Perfusion for assessment of samples with user programmable changing moisture levels
- Vacuum/Pressure ampoules for accurate measurement of pressure changes simultaneous with heat flow measurements
- Easy access points for insertion of probes into sample for powerful integrated multiple signal measurements through user provided probes for monitoring pH, O2, or turbidity concurrent with heat flow

**Features & Benefits:**
- Easy configuration and operation of micro reaction systems with TAM Assistant software thru a multi-channel accessory interface
- TAM IV thermostat will accommodate multiple accessory interfaces for maximum throughput and flexibility
- Up to eight (8) identical or different accessories connected and controlled thru one accessory interface for unmatched flexibility
- Easy configuration of syringe pumps and stirring controls for titration ampoules
- Peristaltic pump or mass flow controller ensures reliable flow for liquid or gas perfusion
- New three channel voltage I/O accessory card for applying or measuring voltage from user configurable probes (pH, O2, etc.)
The TAM IV perfusion micro reaction system is a unique configuration for the continuous flow of a gas or liquid through or over the sample being assayed. With the more complex RH perfusion experimental set-up, an RH perfusion ampoule and gas flow controller are configured together to deliver a controlled stream of gas with a user defined relative humidity over the sample.

**Perfusion Features & Benefits:**
- A liquid or gas is continuously perfused through the ampoule for the study of adsorption, absorption, hydration and swelling
- Optional gas flow controllers ensure easy experimental set-up and enables stability and compatibility measurements under controlled atmospheric conditions
- Optional peristaltic pumps are easily configured for experiments requiring a continuous flow of a liquid
- User choice of reaction vessels in glass, stainless steel and Hastelloy - 1, 4 and 20 mL volumes
- Matrix cartridge holds sample in flow path and maximizes the available surface area for powder sample interactions
- Easy set-up and experiment control with both the gas and liquid flow systems controlled directly via TAM Assistant software
- User configurable stirring and injection capabilities expands the experiment set-up options for unmatched flexibility
- Choice of Nanocalorimeter or Microcalorimeter, depending on sample requirements

**Oxidation of a Polyamide**

Oxidation of a Polyamide 6 film studied by gas perfusion calorimetry at 110 °C. Two Perfusion ampoules were loaded with the same amount of an unstabilized PA 6 film. The first ampoule was perfused with nitrogen and the other one with oxygen and the heat flow was followed for 4 days. The sample under oxygen atmosphere shows a high reaction rate similar to an autocatalytic reaction with no observed induction time. After 4 days the gases were switched, i.e. nitrogen flushing through the first ampoule was replaced with oxygen and oxygen flushing through the second ampoule was replaced with nitrogen. The immediate response when changing the gases clearly shows that the heat flow monitored by TAM is associated with oxidation.

**RH Perfusion Features & Benefits:**
- RH Perfusion reaction vessels available in glass, stainless steel and Hastelloy - 1, 4 and 20 mL volumes
- Easy, user programmable experimental setup with two gas flow paths to the sample - one at 100% RH and one completely dry
- Two built-in humidifying chambers on the ampoule are thermostated to the measuring temperature to ensure 100% saturation of vapor
- User selectable gas mixing to achieve a linear RH ramp or a step change in RH
- All ampoules are compatible with aqueous and organic solvents for use in harsh matrix conditions
- Easiest experiment set-up and data acquisition with both the overall gas flow rate and the relative humidity controlled directly via the TAM Assistant software
- Choice of Nanocalorimeter or Microcalorimeter, depending on sample requirements
- A highly sensitive technique for:
  - Determining sample amorphicity
  - Measuring sample stability and component compatibility
  - Characterizing adsorption, absorption, hydration and swelling

**RH Perfusion: increasing humidity**

Continuous slow increase in humidity over micronized lactose. Several events/transition can be distinguished: (1) Adsorption of water and molecular rearrangement of the sample/water. (2) Crystallization of the amorphic part of the sample. (3) Expulsion of water from the newly created crystal lattice. (4) Polymorph transformation.
Titration Calorimetry is a powerful analytical technique for characterizing a wide range of molecular interactions as well as enzyme and chemical kinetics. The titration reaction systems can be used for injecting one sample into another, such as creating a bioassay for the study of cell metabolism when a drug is injected into a living cell culture. The removable ampoule design of the Titration system provides maximum flexibility to accommodate a wide variety of ITC applications.

**Titration Features & Benefits:**
- Titration performed in a TAM IV calorimeter will accommodate a wide variety of sample configurations
- Solids or powders
- Suspensions
- Aqueous and organic solvents
- Biological and non-biological samples
- Widest range of titration applications easily configured for TAM IV Titration
- Complete thermodynamic characterization of solid or liquid molecular interactions
- Determining thermodynamic binding profiles in one experiment
- Accurate determination of mixing enthalpy
- Ideal technique for determination of dissolution kinetics
- Unique hardware and software capabilities for absorption and swelling measurements
- Maximum sensitivity and sample flexibility for dose-response drug sensitivity assays on viable living cells
- Precision control of titrant delivery for accurately characterizing enzyme and chemical kinetics

**Example: Energetic Material Heat Flow & Pressure**

Heat flow and pressure development are important considerations in evaluating storage safety and stability for materials such as percarbonates, explosives, propellants and other unstable materials that generate gaseous byproducts during decomposition. The vacuum/pressure ampoule permits simultaneous measurement of heat flow and sample pressure in a closed system. The accompanying plot illustrates the heat flow (red) and resulting pressure increase (blue) associated with the decomposition of sodium percarbonate.

**Features & Benefits:**
- Simultaneous measurement of heat flow and pressure up to 10 bar offers reliable safety assessment information on unstable energetic systems
- Built-in relief valves for safe measurements
- Choice of Nanocalorimeter (4 mL) or Microcalorimeter/Multicalorimeter (20 mL), depending on sample requirements
- Optional ampoule holding scaffolding and manifold for easy manipulation or management of initial pressure or vacuum above sample
- Instrument of choice for performing standard methods for energetic material testing:
  - Explosives & propellants
  - Percarbonates
  - Volatile organic solutions
- Highest sensitivity for detecting even small amounts of evolved gas
Solution calorimetry is a powerful technique for characterizing heat transfer between molecules and understanding dissolution phenomena. Two configurations are available: Precision Solution Calorimeter (SolCal) or the Microcalorimeter with a microsolution ampoule.

### Solution Calorimetry Configurations

<table>
<thead>
<tr>
<th>Features</th>
<th>SolCal</th>
<th>MicroSolution Ampoule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Amount (mg)</td>
<td>15-200</td>
<td>50-500</td>
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<tr>
<td>Solvent Volume (mL)</td>
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<td>Length of dissolution process</td>
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<td>Number of samples per run</td>
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<td>Sample ampoules</td>
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<td>Injection cartridge, opens up upon injection</td>
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<tr>
<td>Sample types</td>
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<tr>
<td>Measurements</td>
<td>Heat of dissolution, dilution and wetting</td>
<td>Heat of dissolution, dilution and wetting, dissolution kinetics</td>
</tr>
</tbody>
</table>

### Features & Benefits:
- Highest accuracy and precision provided with SolCal
- Choice of 25 mL or 100 mL SolCal volumes depending on sample requirements
- Microcalorimeter with microsolution ampoule is easily configured for long term dissolution experiments

### Schematic of heat of transfer

Calculations of the enthalpy of transfer between two polymorphs from the heats of solution. By measuring the heat of solution of two different polymorphic forms, it is possible to calculate the transformation enthalpy (ΔH_{trans}) for the transition of form A to form B, taking the difference in the heat of solution between the two forms (ΔH_{sol,A} and ΔH_{sol,B}). The direction of the transition (A to B or B to A) is an indication of the relative stability of the pair and is more likely to occur if the transformation enthalpy is negative (exothermic).

\[
\Delta H_{sol,A} - \Delta H_{sol,B} = \Delta H_{trans,A} \quad (A \rightarrow B)
\]

Polymorph A
Polymorph B
Solution

\[
\Delta H_{sol,A} = \Delta \Delta H_{sol,A,b \rightarrow a}
\]

### Calculations for Entropy

\[
\Delta S_{trans} = \frac{\Delta H_{trans}}{T_f} - \Delta H_{trans} \ln \left( \frac{T_f}{T_i} \right)
\]

where:
- \( \Delta H_{trans} \) is the transformation enthalpy,
- \( T_f \) is the final temperature at equilibrium,
- \( T_i \) is the initial temperature.

### Example

**Problem**: Calculate the entropy change for the transformation of form A to form B at 300 K.

**Solution**:

\[
\Delta S_{trans} = \frac{\Delta H_{trans}}{300} - \Delta H_{trans} \ln \left( \frac{300}{298} \right)
\]

Where:
- \( \Delta H_{trans} \) is the transformation enthalpy.

#### Measuring Heat of Solution

<table>
<thead>
<tr>
<th>Measurements</th>
<th>SolCal</th>
<th>MicroSolution Ampoule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat of dissolution, dilution and wetting</td>
<td></td>
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<tr>
<td>Heat of dissolution, dilution and wetting, dissolution kinetics</td>
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</table>
Pharmaceutical Stability Testing

Isothermal calorimetry can be used to obtain reliable stability data within hours or days and under near ambient storage conditions. Data can be obtained closer to actual conditions than other techniques such as isothermal goniometry. Conventional stability screening methods such as HPLC after long periods of time or months to obtain reliable data.

Isothermal heat flow measurements of pharmaceuticals are a straightforward way to characterize the stability of a drug and its formulation.Isothermal calorimetry can detect both chemical and physical changes within a sample, both being critical for the performance of the pharmaceutical.

Chemical degradation is conventionally studied by HPLC, which has the disadvantage of being relatively insensitive to small changes in concentration. In order to accelerate any degradation reactions taking place in the sample and study the acicline, time-extended temperatures are often used. The data generated when using such accelerated time-lines usually require extrapolation to predict the stability of the temperature selected for storage.

Due to the temperature range and high sensitivity of the TAM for micromolar systems, accelerated conditions are not required. The stability of the TAM thermostat allows even the very slow reaction rates to be detected and accurate and reproducible stability measurements can be made in a short time under typical storage conditions. The data generated in a TAM IV measure the inherent rate encountered when extrapolation of data is required. Thus, microcalorimetry is particularly useful for quantifying very slow reaction rates.

The example shows the oxidation of dl-α-tocopherol at different temperatures (50 °C, 40 °C, 30 °C and 23 °C). As the temperature increases, the heat flow curves get larger in magnitude, i.e. the rate of reaction increases. The heat flow data was fitted for first order kinetics and the rate constant was plotted in an Arrhenius relationship together with HPLC data on the oxidation product. The TAM data (circles) and HPLC data (triangles) fall into the same linear Arrhenius relationship, indicating it is the same reaction being detected, although TAM is capable of detecting the reaction at much lower temperatures.

Polyorphism

An estimated 80% of pharmaceutical compounds exhibit polymorphism, which can manifest itself as a metastable crystalline form. Screening for polymorphism is important because polymorphic transformations have been shown to affect the bioavailability of a compound. The selection of the appropriate crystal form requires a thorough and systematic approach to polymorphism screening. While a lack of chemical change can pose a problem for many analytical probes, TAM can be used to successfully monitor the type of processes continuously over time at or near typical storage temperature. This figure illustrates the isothermal transformation of α-tripalmitin to β-tripalmitin at 35 °C over 50 hours. The green line shows the calculated data from powder X-ray diffraction, and the blue line shows heat flow. The TAM data clearly mimics the calculated data from X-ray diffraction and does so continuously throughout the course of the reaction.

Solvent Mediated Polymorphic Transformation

Polyorphic transformations can occur via two distinct mechanisms. One mechanism is via molecular rearrangements in the dry state and the other is via a solvent phase, i.e. solvent-mediated polymorphic transformation. The solvent-mediated process increases the rate of the process and works by adding a small amount of solvent to the sample. The solvent-mediated transformation is triggered by the addition of solvent, which dissolve the less stable polymorph and crystallize into the more stable form. This reaction will continue until the sample has been completely transformed. The plot shows the polymorphic transformation for different lots of a drug that have been generated with different processes: blue: lot A, green: lot B, red: micronized lot A. The calculated enthalpies are the same, but the reaction rates are different due to differences in the stability of the samples.

TAM Data
HPLC Data


Applications | Pharmaceutical
Hydrate formation in Ethinyl Estradiol

The example shows the humidity dependent hydrate formation in Ethinyl Estradiol. The sample has been exposed to various levels of relative humidity with the use of microhygrostats (blue 100%, red 95%, green 88%). The resulting data clearly shows that the reaction is faster with higher RH.

Heat flow data is related to the rate of reaction, while the integrated heat flow data is related to the extent of the reaction. A plot of heat flow versus heat can be fitted to a kinetic model and the rate constant determined.

The rate constant is plotted against the relative humidity and the critical humidity for this reaction can be determined, (inset in upper plot) i.e. no hydrate will be formed at relative humidities below 84%.

Determination of Solubility

For any new drug it is important to determine the solubility to optimize the formulation and the administration of the drug. Isothermal titration calorimetry can be used to determine solubility with high precision, even for compounds with very low solubility. The example shows the solubility determination of glycine in water. A solubility plot of the sample is placed in the titration ampoule and small amounts of solvent in discrete injections are added to the solution. The first injections show the heat of dissolution. After the solubility concentration has been reached the heat of dilution is measured. The lower plot is heat per injection vs sample in added amount of total solvent.

Amorphicity & Crystallinity

Micronization and processing can alter the surface properties of materials. Small amounts of amorphous material may change the characteristics of the powder in a way that affects both processing and bioavailability. TAM IV is an excellent tool for characterizing low levels of amorphicity in a solid. There are three calorimetric approaches: the microhygrostat method, the controlled relative humidity perfusion method and the solution calorimetry method.

Quantification of Amorphicity– Microhygrostat Method

The sample is isoosotated into an ampoule and then exposed to water (or other solvent) vapor by the use of a microhygrostat with a saturated salt solution giving the desired relative humidity. The solvent lowers the glass transition temperature of the amorphous material enough to induce crystallization, which is monitored as an exothermic response in the microcalorimeter as shown in the upper figure. By integrating the curve the amount of amorphous material in the sample can be quantified to levels around 1%.

Quantification of Amorphicity– Controlled Relative Humidity Perfusion Method

This approach to detect small levels of amorphicity is the most sensitive calorimetric method, where amorphous contents approaching 0.1% can be determined. A small amount of sample is loaded into an RH perfusion ampoule and then exposed to either a continuously increasing humidity or a stepwise increase and decrease in relative humidity. In the example shown, the RH was changed between 30% and 40%. The signal on the increase comes from absorption of water and crystallization of the amorphous material. When the RH is set to 40%, desorption is measured and in the next increase to 40%, only absorption is measured. The difference between peak 1 and peak 3 is a measure of the crystallization heat and can be used to calculate the amorphous content in the sample.

Data provided by L.E. Briggner, AstraZeneca, Sweden (2002)
Quantification of Amorphicity - Solution Calorimetry

Solution calorimetry is an alternative to heat flow microcalorimetry in the assessment of amorphicity. This method works by dissolving the solid material in a solvent and measuring the temperature rise or fall in the solvent as a result of dissolution. Since amorphous and crystalline materials will have a different heat of dissolution, solution calorimetry can be used to quantify the amount of amorphous material in a mixture of the two.

The solution calorimetry method is useful for materials, where crystallisation of the amorphous regions is not possible. It also measures the amorphicity of the whole particle and not only the surface accessible parts.

The first figure shows the solution calorimetry data for a 5% amorphous fraction of lactose. The y-axis shows temperature offset from the bath temperature which was 25 °C. The central “break” section shows the temperature decrease as a result of dissolving the sample in water. The other two steep transitions on either side are calibrations.

The second figure is a calibration curve, where the enthalpy of solution is plotted versus amorphous content and demonstrates the ability of the solution calorimeter to effectively measure lower levels of amorphicity.


Stability of Propellant (gun powder) uUnder Controlled Humidity

Chemical stability is strongly influenced by storage conditions. After temperature, the most important atmospheric conditions for the stability of propellants is humidity. The RH Perfusion Ampoule allows for the atmospheric relative humidity to be controlled and even varied during the course of a heat flow measurement for propellant stability investigations. This control may be used to investigate or simulate storage and shipping conditions. The accompanying plot shows the heat flow from a gun powder sample held isothermally at 37°C and exposed to varying levels of atmospheric humidity. The measured heat flow increased with increasing RH. This higher heat flow at the higher humidity levels reflect lower stability, underscoring the importance of controlled, dry storage conditions.

Efficiency of Stabilizers

Polymers are sensitive to oxygen, however adding small amounts of antioxidants, e.g. radical scavengers and/or hydroperoxide decomposers, can prevent the unwanted oxidation reactions. The oxidation of unstabilised polyamide 6 film (40µm) stabilised with different amounts of a radical scavenger (Irganox 1098) was studied in air at 120˚C. Increasing the ppm of the scavenger from 100 to 400 ppm shows a corresponding decrease in heat flow. The decrease in heat flow is a reflection of an increasing polyamide stability due to the reduction of oxidation. Isothermal microcalorimetry can be used not only to measure oxidation processes, but also to measure the efficiency of different stabilisers, as well as optimizing the amount of stabiliser used in formulating a stable polymer.
Material Compatibility

Compatibility testing is a form of stability testing that evaluates the possible interaction between the constituents of a multicomponent sample. The test is performed to particularly useful for compatibility testing in some cases such as obtained after only a few hours. One example is the non-compatibility between wax and wool. The difference between these measured response and the expected response indicates incompatibility. This type of measurement is broadly applicable for safety screening, is simple to perform, and provides data that can be used for long term storage predictions under many conditions. In addition, it is particularly important that the propellant has no unpredictable interaction with the other non-propellant components. STANAG 4582 cites microcalorimetry as one of the preferred methods to detect such incompatibilities.

Laundry Product Compatibility

Sodium percarbonate, SPC, is used as an insoluble bleaching agent in many applications, e.g. laundry and automatic dishwashing detergents. Detergents usually include a variety of ingredients such as tensides, enzymes and perfumes. In order to increase the efficiency of tensides, inorganic absorbers such as Zeolite are commonly added to trap Ca²⁺/Mg²⁺ in the washing water. However, Zeolite can also trap Na⁺/K⁺ and SPC and both of these are known to reduce the stability of SPC. These tests were performed at 30 °C and with an RH of 70%. The data confirmed that there was an initial reaction when the peroxide and Zeolite were added together that had an initial rapid rate followed by a slowing when the peroxide and Zeolite were added together that had an initial rapid rate followed by a slowing.

Stability of Propellants by STANAG 4582

The evaluation and characterization of the stability of propellants is widely carried out in a STANAG 4582 method following the STANAG 4582 method. This method describes how to test and quantify propellant stability using calorimetry. Selecting a test temperature (T=90°C) will determine the length of the test (usually a few days at 90°C to months at 60°C). During the prescribed evaluation time, the maximum heat flow from the sample that reaches the upper heat flow limit as described by the method. This method can also be used for quality control and surveillance testing in which case the total test time can usually be shortened by 30%. The example in the figure shows data collected from a very stable propellant sample. The heat flow never reaches the upper STANAG limit, and enhanced measurements, optional vacuum/pressure ampoules enable the collection of both heat flow and pressure data.

Stability of Sodium Percarbonate

Sodium percarbonate is manufactured on a vast scale around the world and is a major ingredient in laundry and automatic dishwashing detergents. One of the characteristics of sodium percarbonate is its thermal instability that causes it to undergo continuous degradation. The degradation of percarbonate is accelerated by water, it is common to coat the surface of the percarbonate particles to increase the stability by protecting them from humidity during storage and shipping. The figure shows the results of calorimetric stability tests on uncoated samples of coated and uncoated percarbonate particles using TAM IV at 90°C and humid conditions. The data demonstrated the relative stability of the samples based on the magnitude of the exothermic heat flow. It also demonstrated the repeatability and the excellent long term stability of TAM. Production, storage and shipping environments can be adjusted to ensure the material remains as stable as possible. The graphs in the data sheet were removed from the thermostate and stored in a humidor at 90°C. When the samples were placed back in the thermostate, the signal was measured again and restored to the expected level.
Battery Charge-Discharge Cycling

Both charging and discharging processes for batteries involve an exchange of heat with the surroundings. For rechargeable batteries, it is especially important to monitor the open-circuit circuit discharge processes immediately after charging. For these measurements the battery can be connected directly to a circuit for in situ measurements. The accompanying plot includes data for three cycles of charging, reflected as highly energetic exothermic peaks. The slow self-discharge process immediately afterward was measured to evaluate the charge stability. The TAM IV has the sensitivity and stability to measure the low-energy self-discharge event, the dynamic thermal range to measure the energetic charging process, and the flexibility to accommodate the more sophisticated circuit load measurements.

Battery Open Circuit Discharge

The static self-discharge of a battery is a slow event that reflects the ability of the battery to hold a stable charge under storage conditions. Isothermal microcalorimetry is a non-destructive method for measuring the process accuracy and reproducibility. A large heat flow from the battery under static conditions typically reflects poor stability and most often predicts a short shelf life. In the accompanying figure the static heat flow is shown for an over-sized Li-ion battery connected to a static control measurement. The measured heat flow is proportional to the rate of self-discharge.

Microcalorimetry can be applied to a wide variety of batteries and can provide fundamental information required to develop new battery designs as well as improve the performance of batteries currently in use in addition to whole device testing. Individual component stability and compatibility can be evaluated.

Isothermal microcalorimetry can be used to evaluate and understand:

- Parasitic Reactions
  - If parasitic side reactions can be eliminated or significantly reduced, it is expected that self-discharge and cycle life of the battery can be greatly improved. This reduces the need for over-sizing the battery and thereby reducing the cost.
  - Parasitic reactions are unwanted processes and most often predict a short shelf life.

- Stability and shelf life
  - Self-discharge will show heat production in an open circuit.

- Life Cycle
  - Life cycle performance during charge/discharge cycles.

- Efficiency
  - How much of the total power generated is available for the external device.

- Internal Resistance
  - Depends on temperature, current draw, age, charge cycles etc.

- Performance
  - Depends on the discharge conditions such as the magnitude of the current, the deliverable terminal voltage of the battery, temperature and other factors.

- Quality Control
  - For critical applications, e.g. pacemaker batteries, it is especially important to monitor the internal resistance.

- Development
  - For critical applications, e.g. pacemaker batteries, a fully charged battery in an open-circuit, the measured heat flow is proportional to the rate of self-discharge.

- Safety
  - Due to material incompatibility, it is possible to separate the various contributions and isolate parasitic energy and thereby quantitatively evaluate and understand individual component stability and compatibility.
Isothermal microcalorimetry in biological science has proven to be particularly useful for research characterizing the metabolic activities of living systems and in studies of cellular and biomolecular interactions. Microcalorimetry has the advantage of being general, nondestructive and very sensitive, thus enabling metabolic activities to be monitored, in real time and under a wide variety of conditions, on samples such as intact tissue biopsies or cell cultures and small animals, insects or plants.

Cell Growth - Drug Sensitivity

Assessment of cancer therapeutic drugs with a biosensor has always been an advanced assay that is a powerful tool in determining which drug would potentially be the best for clinical treatment of the diseases. Isothermal microcalorimetry is a fast, easy method for making this assessment. With proper controls being tested simultaneously, isothermal microcalorimetry can detect very small changes in cellular metabolism upon the addition of any selected drug to the growth environment. In the example, methotrexate at a variety of concentrations was added to in vitro cultures of T-lymphoma tumor cells. The resulting metabolic thermograms revealed that on average a single bacteria in an active growth phase will produce a heat flow of approximately 100 μW. Extrapolation of this number suggests that the detection limit in a sample is approximately 10^6 bacterial cells. A wide variety of microorganisms have been evaluated with isothermal microcalorimetry. The method is easy to set up and rapidly detects even slow growing bacteria such as Mycobacterium tuberculosis. Three unique metabolic thermograms are shown (red, blue and yellow), each representative of a different species of bacteria.

Microbial Metabolism

The use of isothermal microcalorimetry in microbiology is a rapidly growing application. The technique has emerged as a very sensitive and rapid method for microorganism detection, possible identification and evaluation of antibiotic susceptibility. Numerous investigations and studies have revealed that on average a single bacteria in an active growth phase will produce a heat flow of approximately 100 μW. Extrapolation of the number suggests that the detection limit in a sample is approximately 10^6 bacterial cells. A wide variety of microorganisms have been evaluated with isothermal microcalorimetry. This method is easy to set up and rapidly detects even slow growing bacteria such as Mycobacterium tuberculosis. Three unique metabolic thermograms are shown (red, blue and yellow), each representative of a different species of bacteria.

Microorganism Detection

Detection and identification of microorganisms in patient blood and donated platelet concentrates is essential in clinical practice to ensure patient care and safety. Commercial blood culture systems are well-established, trusted methods for detecting bacteria in samples such as blood and platelet concentrates. These techniques typically require relatively large sample sizes for testing and the time required for an assay result can be 24-48 hours. Calorimetric detection of microbial growth has been shown in frequent cases to be more sensitive, requiring a smaller sample and giving reliable data in a shorter time (≤10 hrs) than the typical blood culture. The data displayed shows the sensitivity of isothermal microcalorimetry in detecting E. coli that has been spiked into platelet solutions within several hours after starting the assay. Rapidly detecting the exo-slipid bacteria E. coli in platelet preparations is important in establishing maximum storage times for platelets and helping to reduce transfusion related infections.
**Applications | Life Science**

### Biocompatibility

The interaction between biological tissue and artificial materials is becoming increasingly important in the field of bioengineering. One very important medical application where biocompatibility is critical is blood dialysis. Any incompatibilities between hemodialysis membranes and human blood would be very detrimental to this life-saving clinical procedure. One example where isothermal microcalorimetry has been used as an assay to test biocompatibility is in the detection and characterization of the interactions of human granulocytes and a variety of polymer materials that would come in contact with blood cells in a typical dialysis machine. Granulocytes are characterized by a low basal metabolism combined with a large metabolic burst associated with phagocytosis when exposed to foreign particles. In this example, granulocytes are added to different membranes and heat flow is measured. After two hours, zymosan particles are added to induce phagocytosis in the granulocytes. It is demonstrated that the granulocytes exhibit this metabolic burst behavior when exposed to the inert material fluorinated ethylene propylene (FEP) however when exposed to regenerated cellulose (Cu) the metabolic burst was much smaller. This type of direct comparison is important when ranking various polymeric materials for potential uses that involve contact with blood cells.

L. Ljunggren & A. Schön “Biocompatibility of dialysis membranes” Thermometric AN 22030

### Apoptosis

It is well known that an energy burst precedes the metabolic event in growing cells known as programmed cell death (apoptosis). When an apoptotic triggering event happens in a viable cell, the metabolic machinery in the cell is mobilized to provide the energy required for processes such as the destabilization and fragmentation of the cellular DNA and cell death. Thus, a microcalorimetric thermogram is a valuable tool in distinguishing between apoptosis and necrosis, the latter being a reaction to a wide variety of cell insults that usually results in cell death. The data show that within 25 minutes of an addition of a monoclonal antibody anti-FcR, a population of leukemia cells sensitive to the antibody displayed an metabolic energy burst (solid gray line) consistent with the cells entering into the apoptotic cascade toward cell death. The dotted line represents the metabolic activity of leukemia cells when buffer is substituted for the antibody. The actual cell death measured as fragmentation of DNA happened after 16 hours, data not shown.

A. Schön “The use of TAM for the early detection of programmed cell death” Thermometric AN 22030

### Cell Growth - Hormone Stimulation

The analysis of cell growth when assessing the binding properties and metabolic influence of newly developed drugs is a critical step in the drug development pathway. Prior to these cell growth assays, initial studies are typically carried out with cell-free techniques such as ITC. However, after the cell-free phase of testing is complete, the effects of the drug can tested in vivo using tissue biopsies or actively growing cell culture. A wide variety of effects can be expected, including overall metabolic increase or decrease that have been known to cascade to extreme events such as apoptosis. Isothermal microcalorimetry is a highly sensitive technique that has been successfully used as a bioassay for even the smallest change in metabolic activity. The example uses mammalian cells as the target sample and a growth hormone (GH) is added to the cultures of varying concentrations. The upper graph shows the varied metabolic response happening in less than 30 minutes. The heat production increase to various GH concentrations (shown numerically in the figure) can be used to construct dose-response curves. The power of isothermal microcalorimetry is that not only are the early metabolic events captured, but the effect of the growth hormone could be monitored for hours or even days on the same samples.

A. Schön “The effect of human growth hormone on cells” Thermometric AN 22029

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**Applications**

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## Thermostat Specifications

<table>
<thead>
<tr>
<th></th>
<th>TAM IV</th>
<th>TAM IV 48</th>
<th>TAM IV XL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thermal Media</strong></td>
<td>Oil</td>
<td>Oil</td>
<td>Oil</td>
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<tr>
<td><strong>Calorimeter Positions</strong></td>
<td>4</td>
<td>48</td>
<td>6</td>
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<tr>
<td><strong>Temperature Range</strong></td>
<td>4 °C to 150 °C</td>
<td>4 °C to 150 °C</td>
<td>4 °C to 100 °C</td>
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<tr>
<td><strong>Accuracy</strong></td>
<td>&lt; ± 0.1 °C</td>
<td>&lt; ± 0.1 °C</td>
<td>&lt; ± 0.1 °C</td>
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<tr>
<td><strong>Long Term Stability</strong></td>
<td>&lt; ± 100 µ°C/24h</td>
<td>&lt; ± 100 µ°C/24h</td>
<td>&lt; ± 100 µ°C/24h</td>
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<tr>
<td><strong>Scanning Rate</strong></td>
<td>≤ ± 2 °C/h</td>
<td>≤ ± 2 °C/h</td>
<td>N/A</td>
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## Calorimeter Specifications*

<table>
<thead>
<tr>
<th>Calorimeter</th>
<th>Short Term Noise</th>
<th>Baseline Drift</th>
<th>Accuracy</th>
<th>Precision</th>
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<tbody>
<tr>
<td>Nanocalorimeter</td>
<td>&lt; ± 10 nW</td>
<td>&lt; 40 nW/24 h</td>
<td>&lt; 2%</td>
<td>± 100 nW</td>
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<tr>
<td>4 mL Minicalorimeter / Multi</td>
<td>&lt; ± 100 nW</td>
<td>&lt; 200 nW/24 h</td>
<td>&lt; 5%</td>
<td>± 200 nW</td>
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<tr>
<td>Microcalorimeter 20mL</td>
<td>&lt; ± 100 nW</td>
<td>&lt; 200 nW/24 h</td>
<td>&lt; 2%</td>
<td>± 100 nW</td>
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<td>20 mL Minicalorimeter/Multi</td>
<td>&lt; ± 300 nW</td>
<td>&lt; 1 µW/24 h</td>
<td>&lt; 5%</td>
<td>± 300 nW</td>
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<tr>
<td>Microcalorimeter XL</td>
<td>&lt; ± 75 nW</td>
<td>&lt; 1.5 µW/24 h</td>
<td>&lt; 3%</td>
<td>± 1 µW</td>
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<tr>
<td>Macrocalorimeter</td>
<td>&lt; ± 500 nW</td>
<td>&lt; 6 µW/24 h</td>
<td>&lt; 5%</td>
<td>± 3 µW</td>
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### DETECTABILITY

<table>
<thead>
<tr>
<th>Solution Calorimeter**</th>
<th>1.4 mJ</th>
<th>&lt; 0.2%</th>
<th>Q &gt; 100 J:0.02%</th>
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<tbody>
<tr>
<td></td>
<td>Q &lt; 50 J:&lt;±10 mJ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q &lt; 0.1 J:&lt;± 5 mJ</td>
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</table>

*Isothermal Operation*

**Temperature Range 15 °C - 90 °C**

## Microreaction System

<table>
<thead>
<tr>
<th>Microreaction System</th>
<th>1mL</th>
<th>4mL</th>
<th>20mL</th>
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<tbody>
<tr>
<td></td>
<td>Baseline drift µW/24 hours</td>
<td>Short term noise µW</td>
<td>Baseline drift µW/24 hours</td>
</tr>
<tr>
<td>Titrination** (with titration reference)</td>
<td>&lt;0.06</td>
<td>&lt; ± 0.02</td>
<td>&lt;0.08</td>
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<tr>
<td>Liquid Perfusion</td>
<td>&lt;0.8</td>
<td>&lt; ± 0.05</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Gas Perfusion</td>
<td>&lt;2</td>
<td>&lt; ± 1</td>
<td>&lt;2</td>
</tr>
<tr>
<td>RH Perfusion</td>
<td>&lt;2</td>
<td>&lt; ± 1</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Micro Solution</td>
<td></td>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vacuum Pressure</td>
<td>&lt;0.05</td>
<td>&lt; ± 0.2</td>
<td>&lt;1</td>
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*Specifications are based on a balanced calorimeter setup and non-corrected heat flow data*

**Drift specification is per hour**
New Castle, DE USA
Lindon, UT USA
Wakefield, MA USA
Eden Prairie, MN USA
Chicago, IL USA
Costa Mesa, CA USA
Montreal, Canada
Toronto, Canada
Mexico City, Mexico
São Paulo, Brazil

Hüllhorst, Germany
Bochum, Germany
Eschborn, Germany
Wetzlar, Germany
Elstree, United Kingdom
Brussels, Belgium
Etten-Leur, Netherlands
Paris, France
Barcelona, Spain
Milano, Italy
Warsaw, Poland
Prague, Czech Republic
Sollentuna, Sweden
Copenhagen, Denmark

Shanghai, China
Beijing, China
Tokyo, Japan
Seoul, South Korea
Taipei, Taiwan
Guangzhou, China
Petaling Jaya, Malaysia
Singapore
Bangalore, India
Sydney, Australia