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Pharmaceutical applications of calorimetric measurements in the new millennium

Karen C. Thompson*

Merck Research Laboratories, WP78-302, West Point, PA 19486, USA

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Abstract

An overview of the current pharmaceutical applications of calorimetric measurements is discussed with an emphasis on providing references supporting various techniques. Areas where recent reviews of the techniques are available will be noted. In the context of the outlined current utilities, future areas of advancement will be discussed. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Calorimetry review; Pharmaceutical application

1. Introduction

Calorimetric measurements are used extensively throughout the pharmaceutical industry for the characterization of drug substance, excipients and dosage forms, and in support of processes. Some techniques have been used extensively for many years [1–4] and others have more recently found utility as commercial availability and theoretical interpretation have opened new possibilities [5,6]. As the new millennium approaches, the pharmaceutical scientist will continue to look to additional refinements and advances in calorimetric measurements to assist in the rapid screening and development of new pharmaceutical candidates. This review will take a snapshot of the utility of these measurements today in order to place the ideas of the future in their proper context.

* Corresponding author. Tel.: +1-215-652-3531; fax: +1-215-652-5299.
E-mail address: karen_thompson@merck.com (K.C. Thompson)

2. Techniques

Calorimetric measurements involve the measurement of thermal events. These events can be a result of isothermal sample conditioning, temperature perturbation, titration and/or flow chemical perturbation and mechanical perturbation. There is no restriction in this discussion on the nature of the developed substance be it a small organic molecule or a protein; a monomer or a polymer. Calorimetric data are utilized in several facets of drug development including discovery, characterization, formulation development, process development and scaleup. There are several calorimetric techniques that one can utilize and these include isothermal microcalorimetry, differential scanning calorimetry, reaction calorimetry and adiabatic calorimetry, isoperibol calorimetry and modulated DSC. The details of all these techniques will not be provided here but the essence of their utility in pharmaceutical development will be discussed and references will be provided for further investigation.

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Table 1
Calorimetric techniques available to the pharmaceutical scientist

Instruments	Mode of operation/utility	References
Temperature scanning instruments[a]		
Differential scanning calorimetry (DSC)	Energy differences between sample and reference are obtained. Utility — polymorphism, crystallinity, stability, interactions/compatibility, glass transition	[3,4,9–13]
Differential thermal analysis	Temperature differences between sample and reference are obtained. Utility — polymorphism, crystallinity, stability, interations/compatibility, glass transition	[3,4]
Temperature modulated differential scanning calorimetry (MDSC/DDSC)	Sinusoidal modulation of a linear heating or cooling scan which allows for the separation of heat capacity and kinetic components of a conventional DSC scan Utility — polymorphism, crystallinity, stability, interactions/compatibility, glass transition	[5,14,15]
Isothermal instruments[b]		
Batch	Utility — stability, shelf life prediction, decomposition mechanisms can be used to follow relatively slow reactions. Note conditions can be perturbed through challenge with moisture, pH, and gases. With attachments one can conduct heats of solution, reaction, immersion and wetting	[16–21]
Titration	Utility — thermodynamics of binding, adsorption, heats of reaction, heats of dilution, aggregation behavior	[19–21]
Flow	Utility — measurements of heats of adsorption, examination of absorption reversibility and competition, surface properties and steric effects	[1,22]
Heat accumulating instruments[c]		
Batch	Utility — in process characterization, hazards evaluation, heats of solution and heats of reaction	[1,23,75,76]
Titration	Utility — in process characterization, heats of dilution and heats of reaction of relatively fast processes	[1,23,24]

[a] Temperature scan of samples to examine thermal events.
[b] Sample maintained under isothermal conditions and thermal power is measured.
[c] Temperature rise of the system is measured directly. This is accomplished through the prevention or minimization of heat exchange between the sample and the constant surroundings. This technique has the shortest response time of the other instruments.

Several reviews have been written about the various techniques that have been utilized in pharmaceutical development [7–11]. General information about each technique, with references to its use, are listed in the Table 1.

The choice of instrument is governed by the means used to probe the system of interest. The sensitivity of the various instruments has been discussed [24].

3. Pharmaceutical development applications

Calorimetry can be used as a screening tool for the selection of drug candidates. Several authors have published papers concerning the utility of calorimetric measurements as a biochemical screening tool. Studies have been conducted with cells introduced in the calorimeter to examine activity of compounds in model systems [2,25–28]. Structure/function correlations utilizing calorimetric and thermodynamic measurements have been conducted [16,17,29–31]. These studies have been conducted with scanning and titration calorimetry. The utility of the calorimeter to determine thermodynamic parameters for binding, without the constraint of spectroscopic techniques, has been utilized in several systems. Calorimetry studies have been utilized in model systems to provide structure/activity data for drug development [32–35]. These instruments utilize fairly small volumes, have high sensitivity and are capable of running studies over a range of temperatures.

Thermal characterization of the drug substance is supported by various calorimetric and spectroscopic techniques in conjunction with analytical tools such as circular dichroism, spectroscopy, chromatography, powder X-ray diffraction, microscopy and environ-

mental microbalance [36–42]. It is this combination of a variety of tools that provides insight to options available in the drug development process. The drug substance, itself, can have several development concerns associated with it including polymorphism, crystallinity and chemical instability [37,43]. These issues can be examined with calorimetry to assess physical and chemical stability and stabilization mechanisms [44–53]. Isoperibol calorimetry and solution calorimetry can be utilized to determine heats of solution and in conjunction with solubility measurements, can be used to determine the most stable polymorph of the drug substance [37,54,55].

Calorimetry studies assist in the development and characterization of proteins. Differential scanning and titration calorimetry can be used to assess these complex species in conjunction with analytical tools such as circular dichroism, fluorescence, chromatography, light scattering and electrophoretic measurements [56–59]. Studies can also be conducted to study lipid systems and polymers utilized for dosage form development [7,60,61].

Dosage form development involves the combination of the drug substance with components, called excipients that comprise the drug delivery system. This added level of complexity necessitates the development of multiple techniques to assure product performance. Calorimetric techniques continue to have utility in this area and have been reviewed previously [2,8,62,63]. Kinetics of degradation can be characterized with isothermal techniques and have been used to examine solution pH stability profile [49,50], oxidative instability [44,48,52] and drug-excipient compatibility [64–67]. Physical changes as a result of processing have also been examined utilizing calorimetric techniques [18,42].

The impact of moisture on dosage forms and their components has been the subject of several papers [15,42,47,53,68,69]. The impact of moisture on glass transitions in amorphous solids and its relation to dosage form instability has also been the subject of several papers [15,70,71]. In process development for lyophilized formulations, thermal measurements are used to assess lyophilization parameters [72–74].

The characterization of processes for manufacture of dosage forms and active drug utilizes calorimetric measurements. The need to access hazards upon process scaleup and in process design is also an important application [23,75–78]. Isothermal aging calorimetry, reaction calorimetry, high pressure differential scanning calorimetry and syringe injection calorimetry are utilized to assess the hazards in process scaleup and the potential for thermal runaway. Isoperibol calorimetry, heat conduction calorimeters and differential scanning techniques can be utilized to determine heat capacities for process design.

Calorimetric measurements are valuable tools in the development of pharmaceutical products. The utility of these measurements is confirmed by their prevalence in each step of the drug development process.

4. The Future

Many calorimetric techniques are still evolving and the need for instrument calibration methods cannot be over emphasized. An area of further need is to develop theories for the assessment of kinetics from calorimetric data to assist in interpretation of results, especially in isothermal measurements where both physical and chemical changes can be occurring. Current studies have applied isothermal calorimetric techniques to assess chemical changes [79–81] but extension of these studies to the subtle physical changes that occur in dosage forms (for example changes in tablet hardness with aging) need to be further evaluated. Limits of detection and limits of quantitation in the assessment of formulated products also need to be further evaluated — this need is beyond knowledge of the detection limit of the instrument and concerns limits of quantitation in the material to be examined.

The utility of microtitration in the screening of drug candidates has not been fully explored or utilized by the industry. The extention of structure/function correlations in combination with combinatory techniques may be a future avenue that will blossom in the new millennium. To combine combinatory screening techniques and calorimetry, system designs need to be robust, utilize even smaller sample sizes and have more rapid throughput.

Modulated DSC has exploded in its utilization in recent years and this application should continue to grow. Methodology and theory should combine to further extend the utility of this technique. Flow calorimetry has not been used extensively in pharma-

ceutical applications primarily due to limitation on sample size and limitations on cell designs to accommodate a variety of sample geometries. The future will hopefully provide more refined designs to assist in examination of transport mechanisms for dermal and other applications.

Micro DSC techniques have recently become available and may find utility for characterization and assessment of dosage forms. Combination techniques, for example, the combination of DSC with TGA, allow for more information to be generated with even smaller samples. The need to push the limits of detection and sensitivity are waiting around the bend.

The millennium brings a bright future for calorimetric methods and their utility in the development of pharmaceutical products. The field is as varied as the problems that need to be addressed. Innovation, experimentation and theory must all work in parallel to continue the growth of calorimetric measurements in this industry. Bring on the millennium and the new challenges ahead!

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