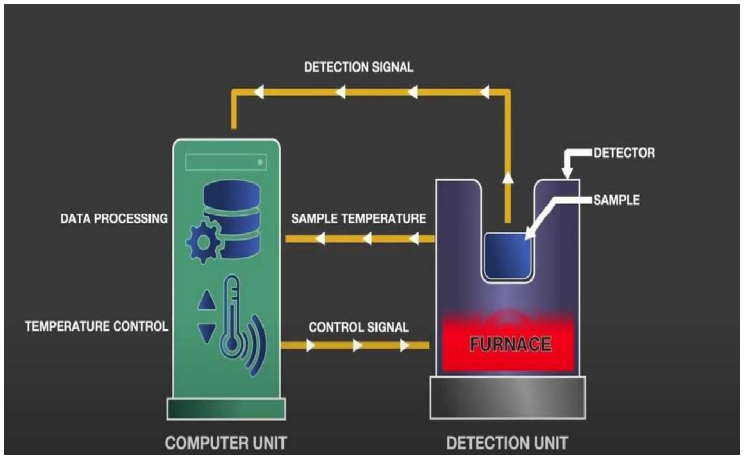
Master 2: Pharmaceutical Chemistry

Module: Drug Analysis and Control

Chapter V. PHYSICAL ANALYSIS FOR MEDICINES QUALITY CONTROL



COURSE.01 THERMAL ANALYSIS IN LEADING PHARMACOPOEIAS.

MELTING POINT DETERMINATION OF API

2023/2024

1. Generality

The development of the pharmaceuticals brought a revolution in human health. These pharmaceuticals would serve their intent only if they are free from impurities and are administered in an appropriate amount. To make drugs serve their purpose various chemical and instrumental methods were developed at regular intervals which are involved in the estimation of drugs. These pharmaceuticals may develop impurities at various stages of their development, transportation and storage which makes the pharmaceutical risky to be administered thus they must be detected and quantitated. For this analytical instrumentation and methods play an important role. This Chapter highlights the role of the physical analytical methods in assessing the quality of the drugs.

1.1. Clinical Drug Trials: The Path to the Patient

The "compound" which is set to become the drug molecule undergoes safety tests and a series of experiments to prove that it is absorbed in the blood stream, distributed to proper site of action in the body, metabolized sufficiently and demonstrates its non-toxicity thus, can be considered safe and successful.

Once the compound is finalized the preclinical research i.e. in vitro studies followed by the animal testing to check kinetics, toxicity and carcinogenicity tests are performed. After passing the pre-clinical tests the regulatory authorities grant permission for the clinical trials.

The clinical trials check whether the drug is working in the proposed mechanism or not, its optimum dose and schedule while the last two stages generate statistically important data about efficacy, safety and overall benefit–risk association of the drug. In this phase the potential interaction of the drug with other medicines is determined and monitors drug's long term effectiveness. After a successful completion of the clinical trials, the drugs are launched in the market for patients. The summary of various stages of clinical trials are listed inTable 1.

Table 1 Summary of phasewise clinical trial and motive of investigation

Phase of clinical trail	Number and type of subjects	Investigation
Phase 1	50–200 healthy subjects (usually) or patients who are not expected to benefit from the IMP	Is the IMP safe in humans? What does the body do to the IMP? (pharmacokinetics) What does the IMP do to the body? (pharmacodynamics) Will the IMP work in patients?
Phase 2	100–400 patients with the target disease	Is the IMP* safe in patients? Does the IMP seem to work in patients?
Phase 3	1000–5000 patients with the target disease	Is the IMP really safe in patients? Does the IMP really work in patients
Phase 4	Many thousands or millions of patients with the target disease	Just how safe is the new medicine? (pharmacovigilance) How does the new medicine compare with similar medicines?

Source: guidelines in clinical trials: 2007 edition. The Association of the British Pharmaceutical Industry, 12 Whitehall London.

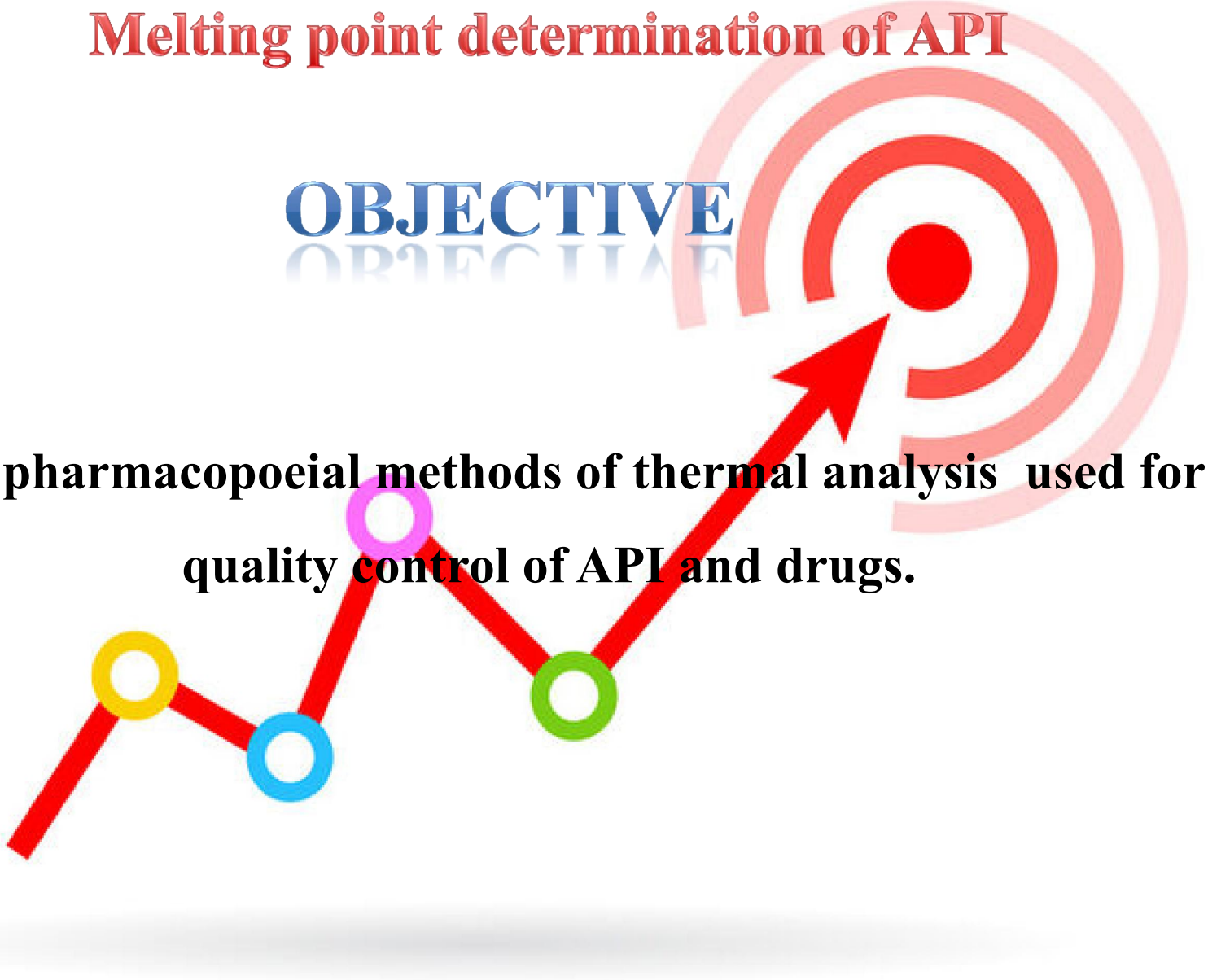
* IMP: investigational medicinal product i.e. the newly developed drug.

From the stages of drug development to marketing and post marketing, analytical techniques play a great role, be it understanding the physical and chemical stability of the drug, impact on the selection and design of the dosage form, assessing the stability of the drug molecules, quantitation of the impurities and identification of those impurities which are above the established threshold essential to evaluate the toxicity profiles of these impurities to distinguish these from that of the API, when applicable and assessing the content of drug in the marketed products. The analysis of drug and its metabolite which may be either quantitative or qualitative is extensively applied in the pharmacokinetic studies.

This chapter highlights the role of various physical analytical techniques and their corresponding analytical methods in the analysis of pharmaceuticals.

2. Thermal analysis in leading pharmacopoeias. Melting point determination of API

OBJECTIVE



to study pharmacopoeial methods of thermal analysis used for the quality control of API and drugs.

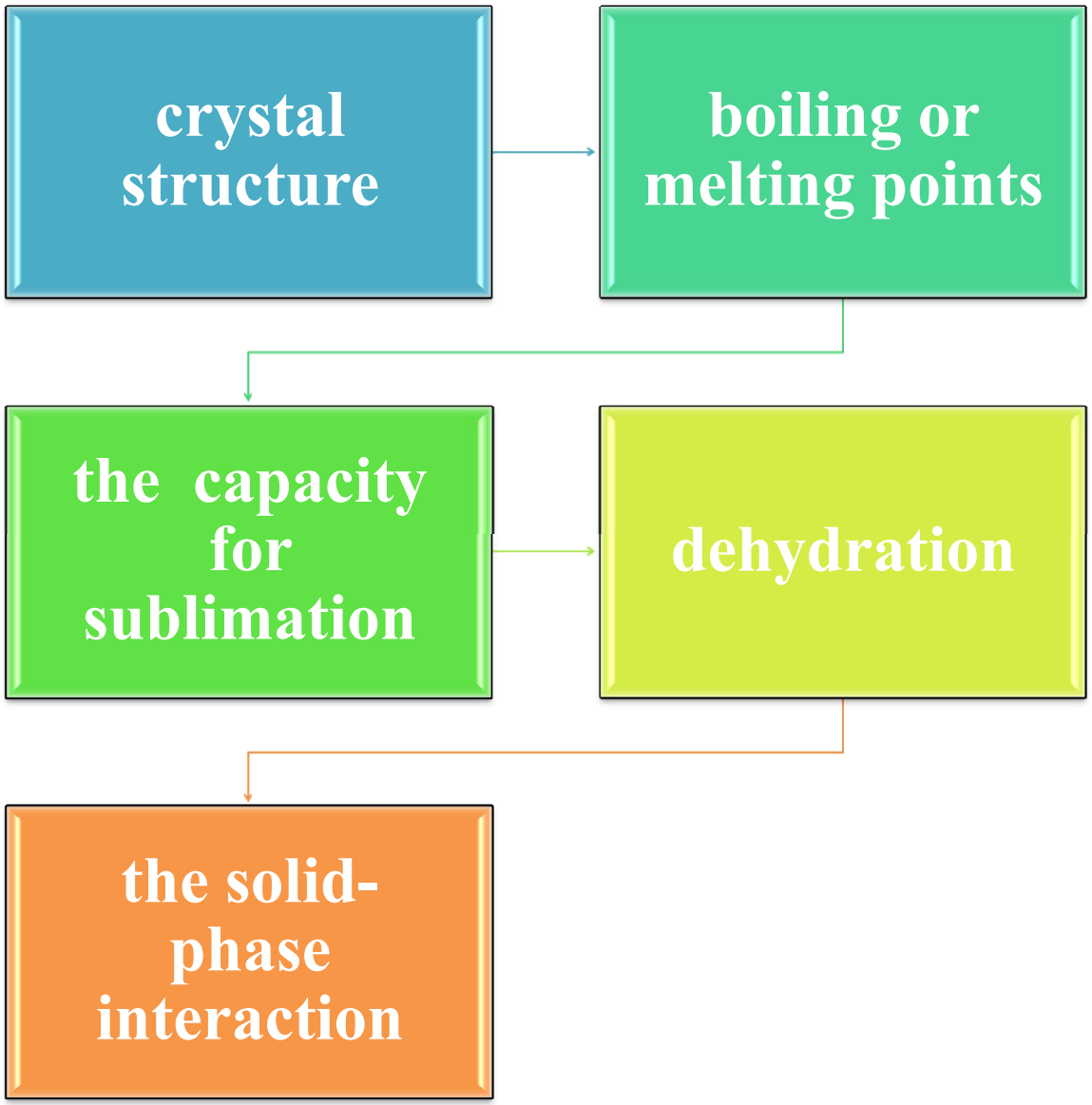
2.1. Introduction

Thermal processes such as chemical reactions, phase transition or loss of crystallization water are always accompanied by more or less significant changes of enthalpy (ΔH). The conversion can result in either the absorption of heat – an endothermic process, or heat release – exothermic process. These thermal effects are detected by means of thermal analysis.

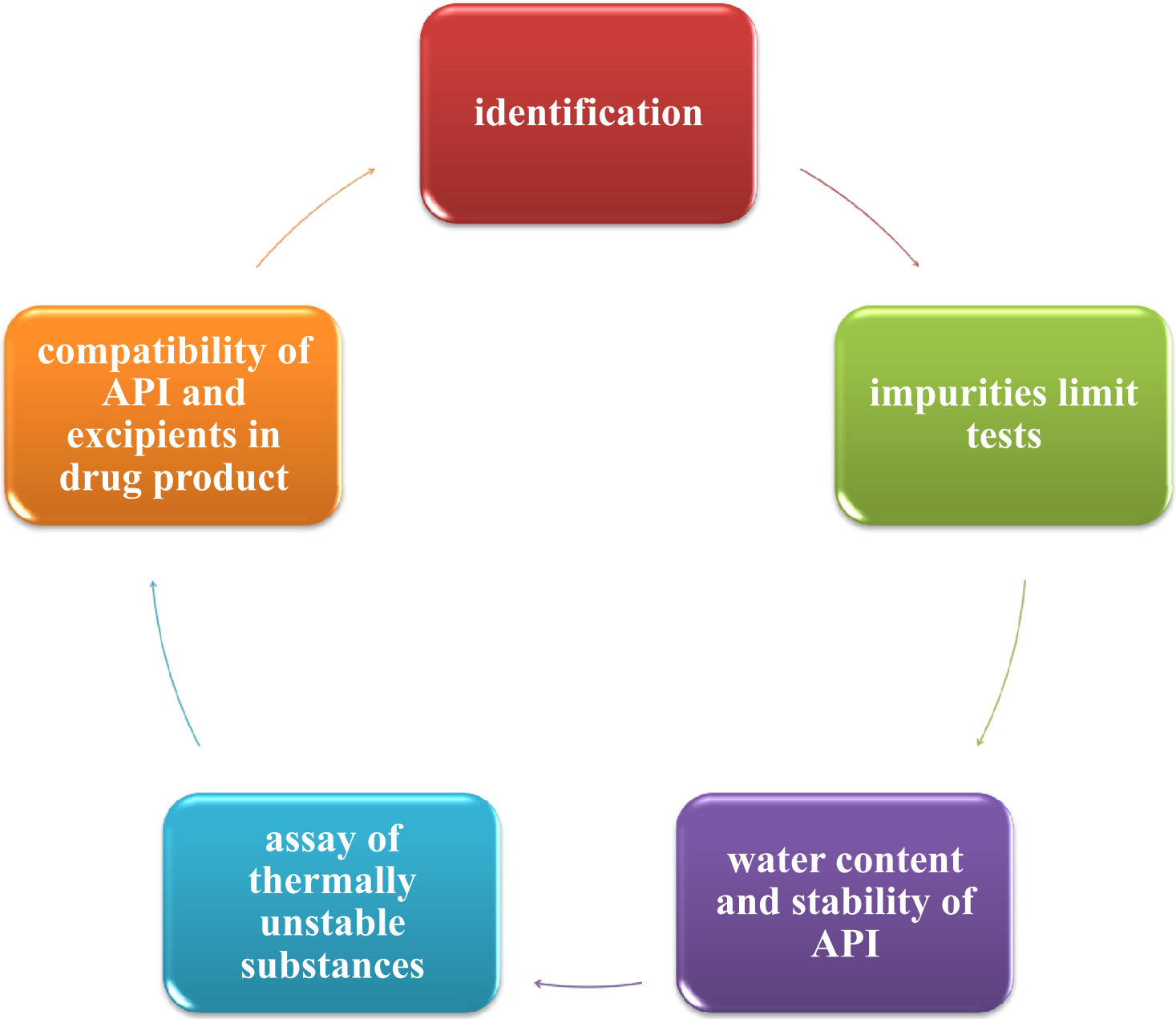
Thermal analysis is the general name of techniques for investigating physicochemical and chemical processes, based on detection the thermal effects that accompany the transformation of a substance under temperature programming conditions. Temperature change can be achieved by heating or cooling at a specified speed, or a combination of different modes. A characteristic feature of thermal analytical methods is their versatility.

Thermal Analysis (TA) is a group of techniques that study the *properties of materials as they change with temperature*

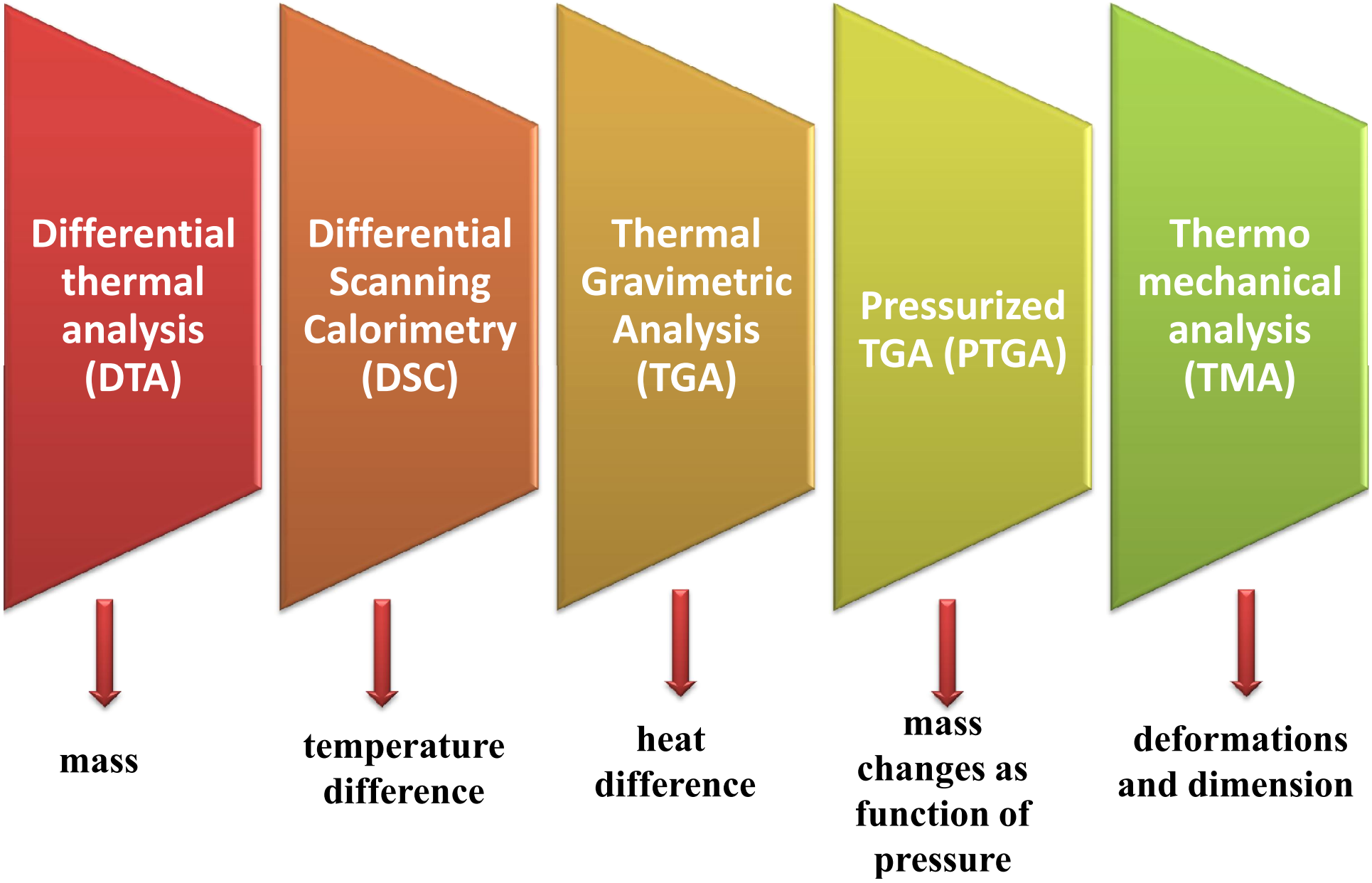
Instrumental methods of thermal analysis provide information about:



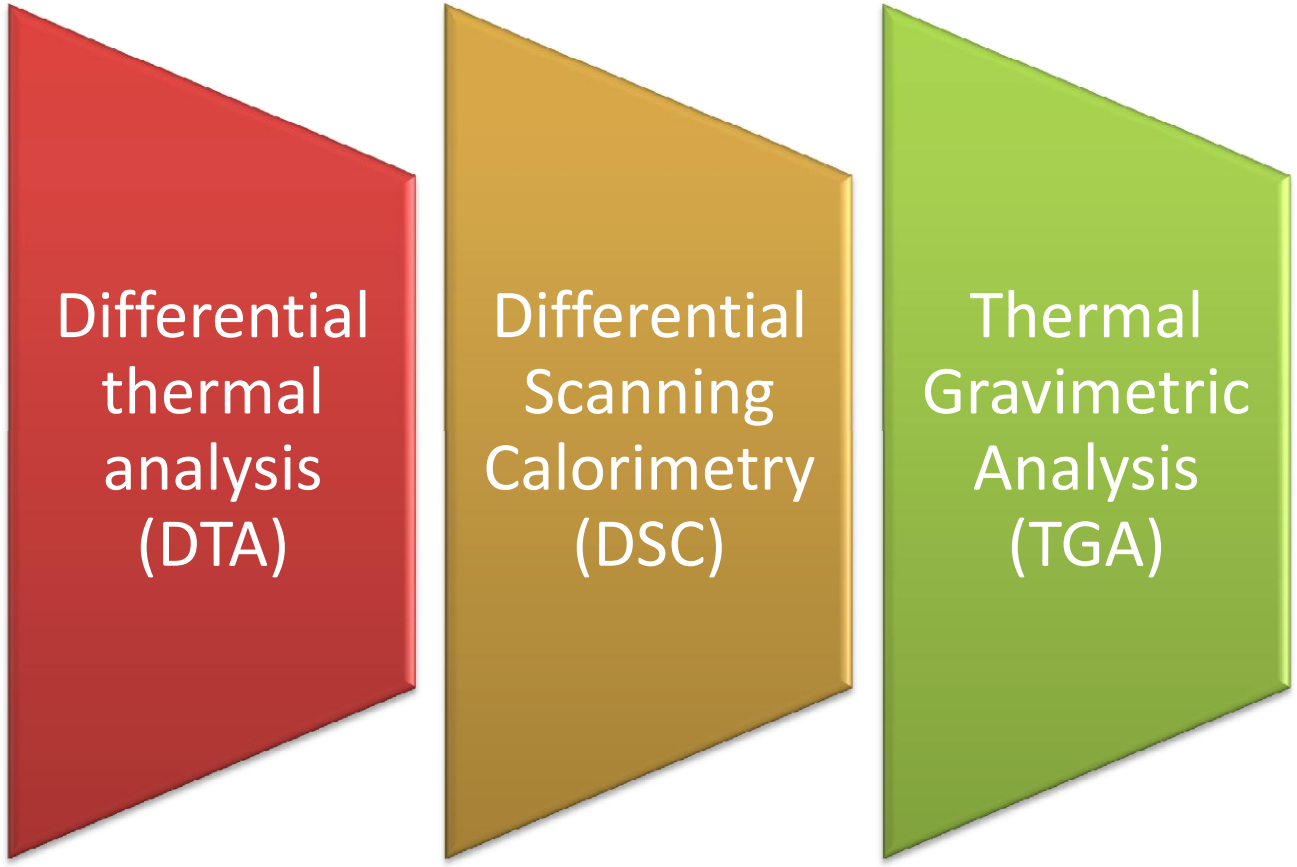
This information can be applied for



Includes several different methods. These are distinguished from one another by the property which is measured

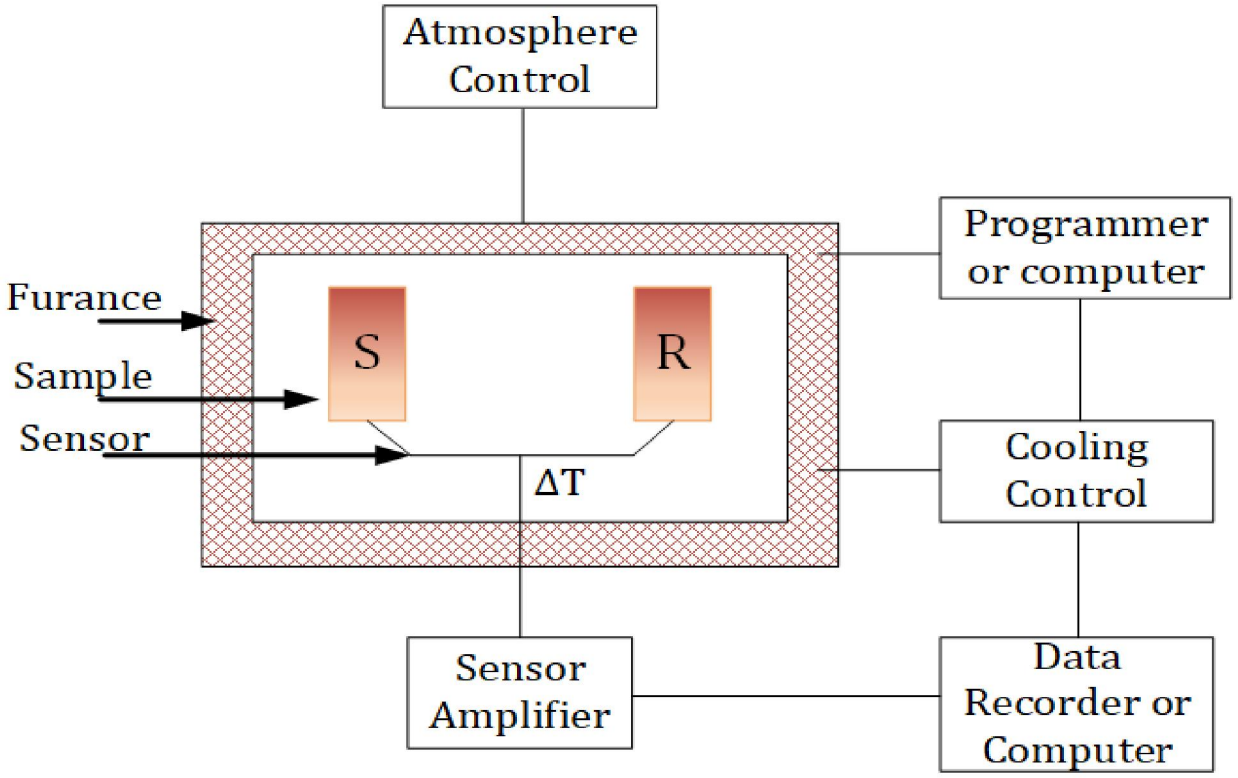


In pharmacopeial thermal analysis (general chapter «Thermal analysis» – Ph. Eur., JP, USP) three methods are used :



2.2. Differential Thermal Analysis (DTA)

Differential thermal analysis is a technique in which the temperature of the substance under investigation is compared with the temperature of a thermally inert material such as α-alumina and is recorded with furnace temperature as the substance is heated or cooled at a predetermined uniform rate.



DTA, Basic

The difference of the temperatures is registered parameter, measured by heating or cooling the sample at a constant rate, which can be represented as a function of the temperature of the sample, standard material or heater. Temperature changes of the sample caused by the phase transitions or chemical reactions associated with the change of enthalpy. These are: phase transitions – melting, alteration of the crystal structure, boiling, sublimation and evaporation, chemical reactions – dehydration, dissociation, decomposition, oxidation, reduction, etc. These transformations are accompanied by the absorption or release of heat. In general, phase transitions, dehydration, reduction, and some decomposition reactions are accompanied by endothermic effects, crystallization, oxidation and some degradation processes – exothermic

DTA; Phenomena causing changes in heat / temperature

Physical

Adsorption (exothermic)

Desorption (endothermic)

A change in crystal structure
(endo – or exothermic)

Crystallization (exothermic)

Melting (endothermic)

Vaporization (endothermic)

Sublimation (endothermic)

Chemical

Oxidation (exothermic)

Reduction (endothermic)

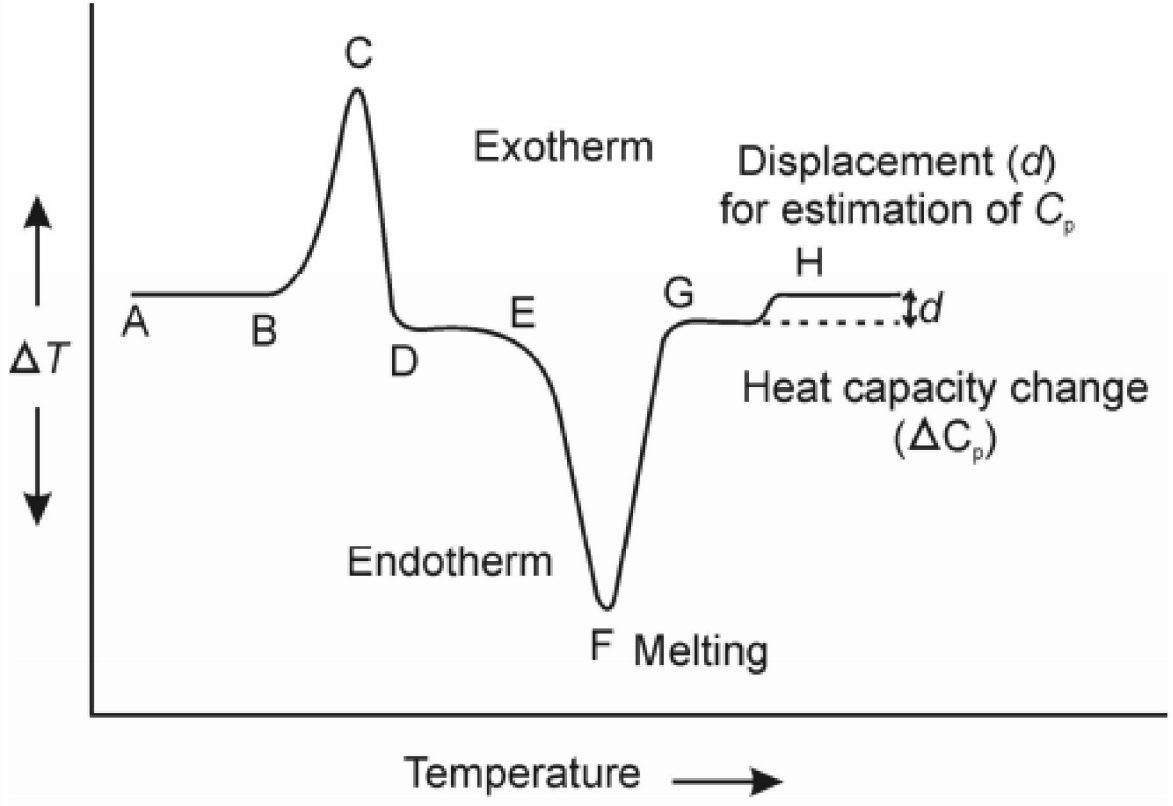
Break down reactions
(endo – or exothermic)

Chemisorption (exothermic)

Solid state reactions
(endo – or exothermic)

Characteristics of DTA Curves

An idealized representation of the two major processes observable in DTA is illustrated in Fig., where ΔT is plotted on y-axis and Ton x-axis. Endotherms are plotted downwards and exotherms upwards. Similarly, the temperature of the sample is greater for an exothermic reaction, than that of the reference, for endotherms the sample temperature lags behind that of the reference.



A representation of the DAT Curve showing exotherm, endotherm and base line changes

When no reaction occurs in the sample material, the temperature of the sample remains similar to that of reference substance. This is because both are being heated exactly under identical condition i.e. temperature difference ΔT (Ts –Tr) will be zero for no reaction. But as soon as reaction starts, the sample becomes either hot or cool depending upon whether the reaction is exothermic or endothermic. A peak develops on the curve for the temperature difference ΔT against temperature of furnace or time.

The number, shape and position of the various exo- and endothermic peaks with respect to the temperature scale is the identification of a substance. Since the area of the peak is proportional to the change in enthalpy ΔH, DTA method can be used for semi-quantitative, and in some cases for quantitative evaluation of the heat of reaction.

$$\text{Peak area (A)} = \pm \Delta H \, m \, K$$

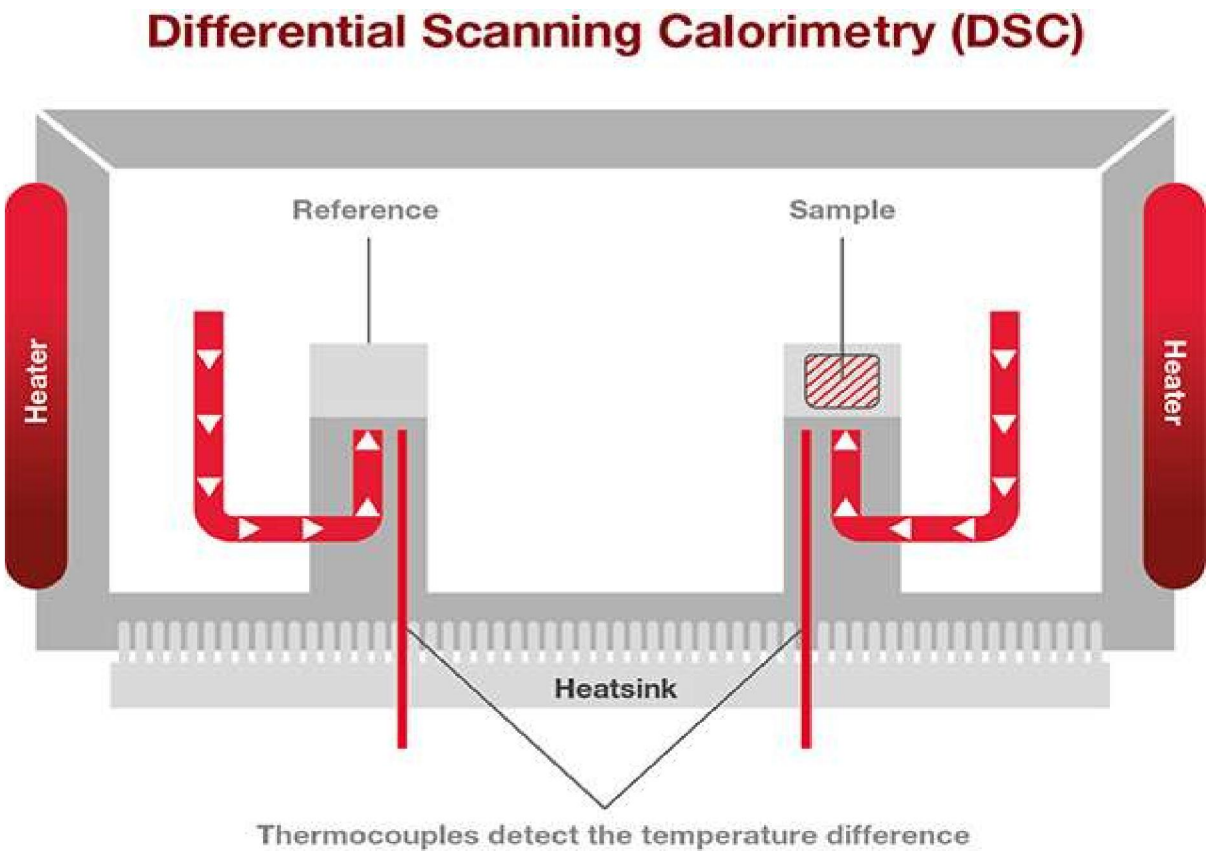
m : mass of sample

K : calibration factor

Δ H : heat of reactions (enthalpy change)

2.3. Differential Scanning Calorimetry (DSC)

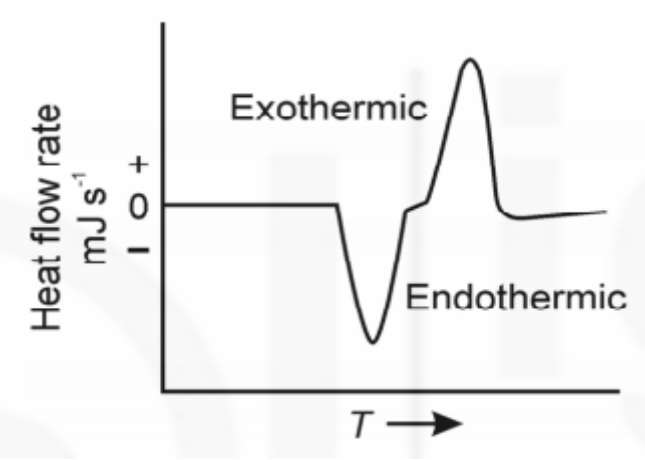
In previous section we have studied DTA techniques. In these methods, thermal reactions are observed by measuring the deviation of the sample temperature from that of the reference material. There is another technique called Differential Scanning Calorimetry (DSC) which have the advantage of keeping the sample and reference at the same temperature and heat flow into sample and reference is measured. This can be achieved by placing separate heating devices in the sample and reference chambers. This is in contras to the DTA scheme, where both sample and reference are heated by the same source.



Differential Scanning Calorimetry

DSC, Basic

In DSC the heat flow is measure and plotted against temperature of furnace or time to get a thermogram. This is the basis of Differential Scanning Calorimetry (DSC). The curve obtained in DSC is between dH/dt in mJs-1 or mcals-1 as a function of time or temperature. A typical DSC curve is shown in Fig. 11.11. The deviation observed above the base (zero) line is called exothermic transition and below is called endothermic transition. The area under the peak is directly proportional to the heat evolved or absorbed by the reaction, and the height of the curve is directly proportional to the rate of reaction. Therefore Eq.11.1 is equally valid for DSC scheme also. The only difference is the calibration factor K in case of DSC is independent of temperature. This is a major advantage of DSC over DTA.



DTA and DSC methods allow us to study the changes in the drug during polymorphic transformations at different heating rates. Thus, for example, one can determine the heating rate, which is necessary to ensure a polymorphic purity of the product (it is sometimes necessary to provide the rate up to 750 °C/min).

2.4. Thermo Gravimetric Analyis

is a technique in which the mass of a sample of a substance is recorded as a function of temperature according to a controlled temperature programme. Which means it measures changes in weight in relation to changes in temperature.

The measured weight loss curve gives information on:

- **changes in sample composition**
- **thermal stability**
- **kinetic parameters for chemical reactions in the sample**

A derivative weight loss curve can be used to tell the point at which weight loss is most apparent.

TGA; Phenomena causing mass changes

Physical

Gas adsorption

Gas desorption

Phase transitions

- Vaporization
- Sublimation

Chemical

Decomposition

Break down reactions

Gas reactions

Chemisorption
(adsorption by means of chemical instead of physical forces)

TGA: Applications

- Characterization of
  - Thermal stability
  - Material purity
  - Determination of humidity
- Examination of
  - » Corrosion studies (e.g. oxidation or reactions with reactive gases)
  - » Gasification processes
  - » Kinetic processes

TGA

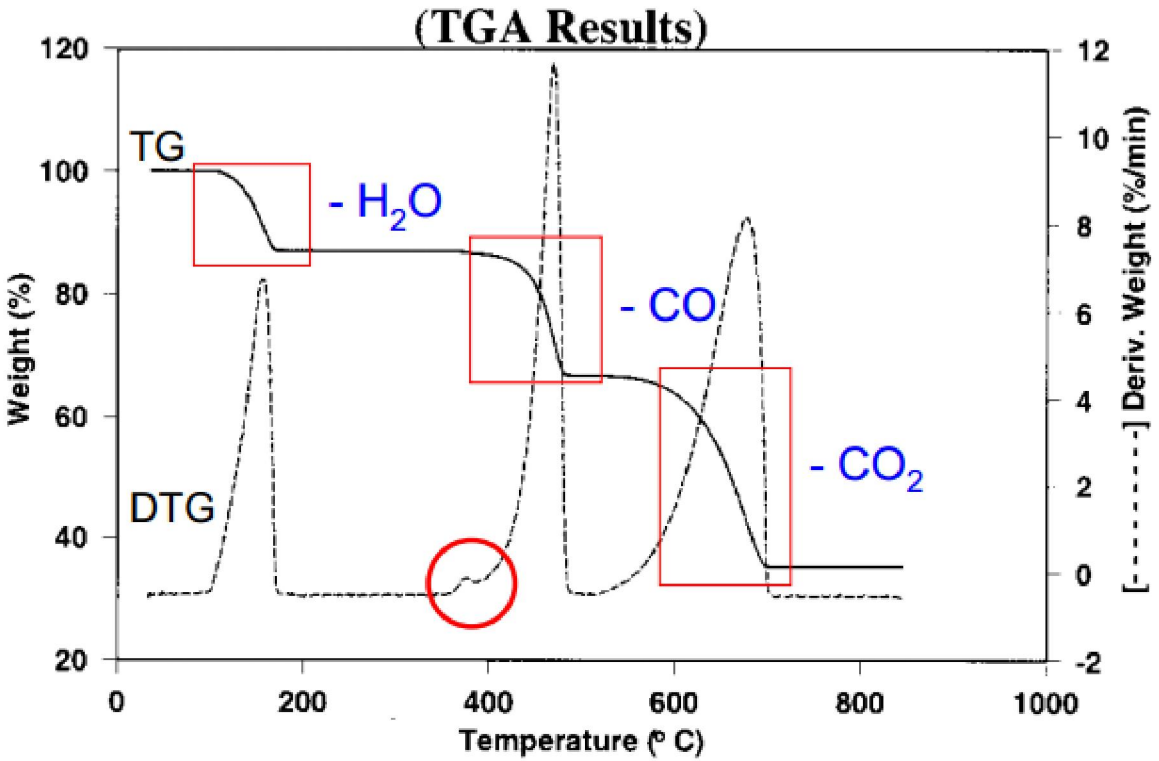
Ex. Decomposition of calcium oxalate monohydrate

- Calcium oxalat monohydrat, a standard material often used to demonstrate TGA performance.

- Exhibits three weight losses with temperature in an inert atmosphere (e.g. N_2).

$$CaC_2O_4 \cdot H_2O \xrightarrow{-H_2O} CaC_2O_4 \xrightarrow{-CO} CaCO_3 \xrightarrow{-CO_2} CaO$$

Ex. Decomposition of calcium oxalat monohydrate



Common gaseous components originating from inorganic materials that decompose before the melting point:

H_2O, CO, CO_2, SO_x, NO_x, Cl_2, F_2, CH_3OH, etc.

Also some chemical reactions in solid phase result in gaseous weight loss ex.

$$Na_2CO_3\,(s) + SiO_2\,(s) \rightarrow Na_2SiO_3\,(s) + CO_2\,(g)$$

Factors affecting the TG curve

Heating rate
Sample size

Increases the temperature at which sample decomposition occurs.

Particle size of sample
Packing
Crucible shape
Gas flow rate

Affects the progress of ther reaction