PharmacoLearn

MPG101T Modern Pharmaceutical Analytical Techniques, M.Pharm Semester 1

Unit 6: Potentiometry and Thermal Techniques

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6.1 Potentiometry

Potentiometry measures the potential (voltage) of an electrochemical cell at effectively zero current, and relates it to the concentration of a specific ion through the Nernst equation: E = E0 plus (RT divided by nF) times the natural log of the ion activity, which at 25 degrees Celsius becomes a change of about 59.16 mV for every ten fold change in activity of a singly charged ion. The cell has two electrodes: an indicator electrode whose potential responds to the analyte, and a reference electrode (saturated calomel or silver silver chloride) whose potential is constant.

Ion selective electrodes (ISE) are indicator electrodes whose membrane responds mainly to one ion: the glass electrode for pH and H+, the fluoride electrode with a lanthanum fluoride crystal membrane, crystalline and liquid membrane electrodes for ions such as calcium, nitrate, potassium and chloride, and gas sensing electrodes for ammonia and carbon dioxide. A practical assembly combines both electrodes in one combination probe with a meter reading in mV or directly in pH or concentration units; calibration with at least two standards bracketing the sample is essential, and an ionic strength adjuster keeps activity coefficients constant. Applications: pH measurement and potentiometric titrations (acid base, redox, precipitation and complexometric, where the end point is the steepest jump in potential), direct assay of fluoride and other ions in formulations and water, and monitoring of dissolution media. Its strengths are simplicity, low cost and no need for separation; its limits are interference from similar ions and the need for frequent calibration.

6.2 Thermal techniques: DSC, DTA and TGA

Thermal analysis studies how a sample changes when it is heated or cooled at a controlled rate. In pharmacy it answers questions no spectrum can: at what temperature the drug melts, whether it is polymorphic, whether it is crystalline or amorphous, whether drug and excipient interact, and how much solvent or moisture it holds.

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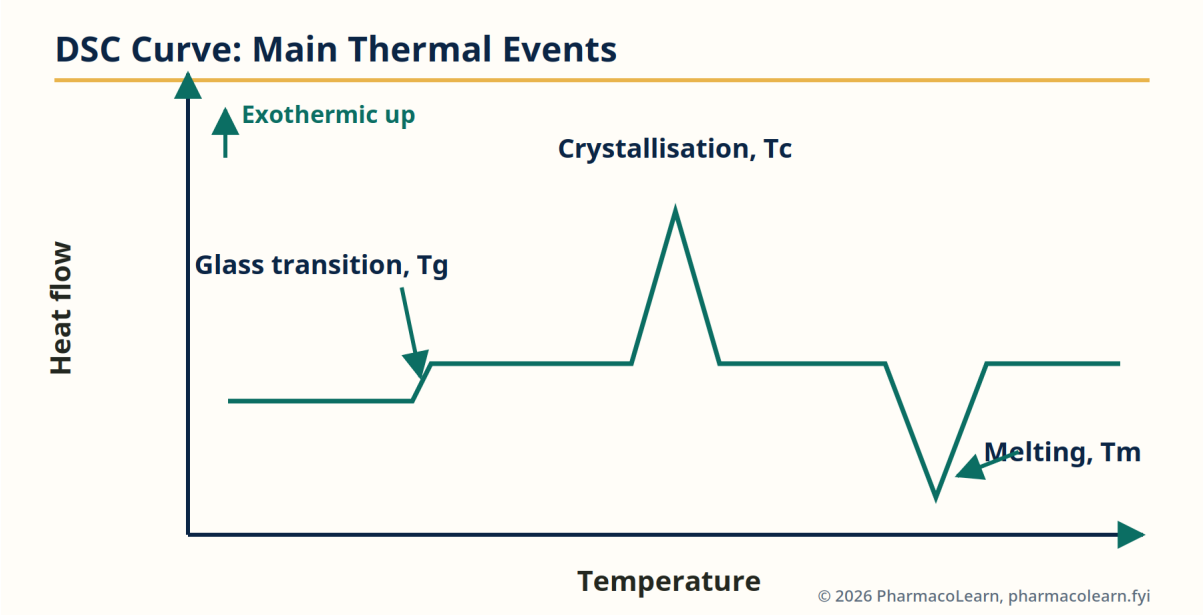

Figure: DSC curve with glass transition, crystallisation and melting events, exothermic direction up.

Differential scanning calorimetry (DSC): the sample and an inert reference are heated in separate pans, and the instrument measures the difference in heat flow needed to keep both at the same temperature as the furnace temperature rises at a linear rate. In the **power compensation** design two independent heaters supply that heat directly; in the **heat flux** design both pans sit on one heated disc and the temperature difference between them is converted into heat flow. The DSC curve plots heat flow against temperature: melting and other endothermic events appear as peaks in one direction, crystallisation and decomposition (exothermic events) in the other, and a **glass transition** appears as a step change in the baseline, the signature of an amorphous material. Two refinements from the syllabus: **modulated DSC** superimposes a small sinusoidal temperature oscillation on the ramp, which separates overlapping reversing events such as glass transition from non reversing events such as enthalpy relaxation and curing; **hyper DSC** uses very fast heating rates (hundreds of degrees per minute) to increase sensitivity for tiny samples and weak transitions and to suppress reorganisation during the scan.

Experimental parameters that influence a DSC result, and which must be reported with it: sample preparation and mass (usually 2 to 10 mg, sealed, pin holed or open pan as the study needs), heating and cooling rate (faster rates raise observed transition temperatures and reduce resolution of close events, slower rates do the opposite), purge gas and its flow (nitrogen is standard; oxygen is used for oxidation studies), calibration with standards such as indium (melting point and heat of fusion) for temperature and enthalpy, and the thermal history of the sample itself, which is why a first heating run and a second heating run of the same sample can differ. Sources of error include poor pan contact, moisture loss mistaken for a transition, decomposition overlapping melting, and baseline drift.

Differential thermal analysis (DTA): the older and simpler relative of DSC. Sample and reference sit in the same furnace and the temperature difference between them (delta T) is plotted against furnace temperature. When the sample melts it absorbs heat and lags behind the reference; when it crystallises or oxidises it gets ahead. DTA gives transition temperatures and a qualitative picture up to very high temperatures, but it does not measure energy as directly or as accurately as DSC. **Derivative DTA (DDTA)** plots the derivative of the DTA curve, which sharpens overlapping events and locates transition points more precisely.

Thermogravimetric analysis (TGA): a sensitive microbalance weighs the sample continuously while it is heated in a controlled atmosphere. The TGA curve plots mass (or percentage mass) against temperature,

and its derivative (DTG) marks the temperatures of fastest mass loss. Mass falls in steps when volatile components leave: surface moisture first, then solvent of crystallisation, then decomposition products. Factors affecting TGA results: heating rate, atmosphere (air gives oxidative loss, nitrogen gives pyrolysis), sample mass and particle size, crucible type, and buoyancy effects at the start of the run. It measures only events that change mass, so melting without decomposition is invisible to TGA, which is exactly why DSC and TGA are run together as complementary methods.

Feature	DSC	DTA	TGA
Quantity measured	Difference in heat flow	Difference in temperature	Change in mass
Melting point	Yes, with enthalpy of fusion	Yes, temperature only	No, unless mass is lost
Glass transition	Yes, clear step	Weak or unclear	No
Moisture and solvent content	Indirect	Indirect	Yes, directly from mass loss steps
Polymorphism study	Yes	Yes	No
Main pharmac eutical uses	Melting, purity, polymorphism, compatibility, amorphous content	High temperature transitions, qualitative thermal profile	Drying loss, solvates and hydrates, decomposition, ash related work

Pharmaceutical applications of thermal methods, combined: drug excipient compatibility screening from changes in the drug melting peak, polymorph identification (different forms melt differently), determination of purity from melting point depression (the Van't Hoff DSC purity method), amorphous content measurement, stability prediction, characterisation of lipids, waxes and polymers used in formulations, and confirmation of hydrate and solvate stoichiometry by matching TGA mass loss with theory. Advantages: tiny samples, speed, and information about physical form that chemical assays miss. Disadvantages: destructive for the portion tested, results depend strongly on experimental conditions, and overlapping events can be hard to assign without a supporting method such as hot stage microscopy or XRPD from Section 5.3.

Frequently Asked Questions

Q: Write the Beer-Lambert law and list any four reasons for deviation from it. The law states A = epsilon x b x c, where absorbance is directly proportional to molar absorptivity, path length and concentration. Deviations occur when the radiation is not monochromatic, when stray light reaches the detector, when the solution is too concentrated so molecules interact with each other, and when the solute associates, dissociates or reacts with the solvent or changes form with pH.

Q: What are the advantages of FT-IR over a dispersive IR spectrophotometer? FT-IR measures all frequencies at once through an interferometer (Fellgett or multiplex advantage), passes more radiation to the detector because it has no narrow slits (Jacquinot or throughput advantage), and uses a laser reference for a highly accurate wavenumber scale (Connes advantage). The result is a spectrum in seconds with a much better signal to noise ratio.

Q: What is chemical shift? Why is TMS used as the reference in NMR? Chemical shift is the position of an NMR signal on the delta scale in ppm, measured relative to TMS, and it tells the electronic environment of the protons. TMS is used because its 12 protons are equivalent and give one sharp strong signal, it is chemically inert and volatile so it can be removed easily, and its signal appears upfield of almost all sample

signals.

Q: A proton NMR signal is a quartet and another is a triplet, with the same J value. What does this tell you? The two groups are coupled to each other. By the n+1 rule, the quartet has three equivalent neighbouring protons and the triplet has two, the classic picture of an ethyl group, CH3 giving the triplet and CH2 giving the quartet. Equal J values confirm they are mutual coupling partners.

Q: Compare EI and ESI ionisation in mass spectroscopy. Electron impact is a hard ionisation using 70 eV electrons on vaporised samples; it fragments the molecule heavily, which is useful for structure work but the molecular ion may be weak or absent, and the sample must be volatile. Electrospray is a soft ionisation from liquid solution at atmospheric pressure; it gives strong molecular species, often multiply charged, with little fragmentation, and it suits polar, large and heat sensitive molecules in LC-MS.

Q: How does the presence of chlorine or bromine show up in a mass spectrum? Chlorine occurs as mass 35 and 37 in about a 3:1 ratio, so a compound with one chlorine shows M and M+2 peaks in that ratio. Bromine occurs as mass 79 and 81 in about a 1:1 ratio, so one bromine gives M and M+2 peaks of almost equal height. These isotope patterns are the quickest way to spot a halogen in an unknown compound.

Q: Define resolution, plate number and HETP. What resolution value means baseline separation? Plate number N measures column efficiency, N = 16 (tR/W) squared. HETP is the column length divided by N, and a smaller HETP means a better column. Resolution Rs compares the separation of two peak maxima with their widths, and Rs of 1.5 or more means the two peaks are separated to the baseline, the standard target in pharmaceutical methods.

Q: Why is reversed phase HPLC used more than normal phase HPLC in quality control? In reversed phase HPLC a non polar C18 stationary phase is used with a water based polar mobile phase, which suits most drugs, gives reproducible retention, is compatible with aqueous samples and dissolution media, and the columns are robust and long lived. Normal phase with bare silica is very sensitive to traces of water in the mobile phase, which makes retention drift, so it is reserved for special cases.

Q: State Bragg law and give two pharmaceutical applications of X-ray diffraction. Bragg law states n lambda = 2d sin theta, relating the wavelength, the spacing d between crystal planes and the angle theta at which diffraction occurs. Its main pharmaceutical uses are identification and quantification of polymorphs by powder diffraction, and complete three dimensional structure determination of drug molecules by single crystal diffraction.

Q: What is isoelectric focusing? Isoelectric focusing is electrophoresis in a stable pH gradient. A protein migrates until it reaches the pH equal to its isoelectric point, where its net charge becomes zero and it stops, focused into a sharp band. It separates proteins with very small differences in isoelectric point and is used for charge variant profiling of proteins and monoclonal antibodies.

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