Applications of ATR UV/vis spectroscopy in physical form characterisation of pharmaceuticals

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Introduction

The application of experimental methods for increasing efficiency and throughput at all stages of the drug discovery and development process is an important goal within the pharmaceutical industry. Key to successful product development is the early selection of the most appropriate solid-state form of the active ingredient to be used in the final dosage form. The need to maximise the efficiency of all steps in physical form screening is therefore driven by the requirement to take the required physical form (polymorph, solvate or salt) of an active ingredient to market in the minimum amount of time. Physical form screening includes systematic searches for:

- pharmaceutically acceptable salts of the active ingredient in order to optimise key physical properties, particularly solubility, dissolution rate and hygroscopicity;
- polymorphs and solvates of the target molecule and the characterisation of the relationships between all forms, typically to identify the most thermodynamically stable form.

Screening methodologies rely on systematically fingerprinting samples recrystallised under a wide range of conditions using spectroscopic, thermal and diffraction techniques. In recent years, considerable effort has been put into developing high-throughput, automated approaches to both salt and polymorph screening and such methods are capable of producing and identifying large numbers of samples in a relatively short period of time. It is vital therefore to ensure that the additional analytical approaches required to provide a complete characterisation of the physical properties of novel crystalline forms, do not form a bottle-neck in the development process.

Here we describe the application of ATR UV spectroscopy in physical form characterisation in the specific context of our work under the auspices of a UK Research Councils' Basic Technology Programme award. The project, entitled "Control and Prediction of the Organic Solid State" is co-ordinated by Professor S.L. Price at University College London and involves experimental screening and characterisation of polymorphs of organic solids.

UV/vis spectroscopy

Given the popularity of tablets and capsules, i.e. solid dosage forms, solubility and specifically equilibrium saturation solubility, C_s, and dissolution rate, J, are key properties of pharmaceutical raw materials in the solid state. For example, a knowledge of these properties allows judgements to be made on the optimal particle size distribution required or the need for salt formation. Traditional methods for determining C_s and J rely on dissolving an excess of powder under constant temperature and stirring rate in a suitable solvent, often an aqueous medium. Where the molecule contains a chromophore, UV/vis absorbance is used to quantify the dissolved concentration throughout the duration of the experiment and identify the point at which equilibrium is reached. However, these experiments are carried out in the presence of an excess of solid (suspended particles) which would otherwise interfere with transmission measurements. These must be removed by filtration before transferring the clarified sample manually or via a flow-throw system to a transmission cell for analysis. Such

Table 1. Data collections parameters for examples in Figures 1–3.

Parameters	Carbamazepine	Theophylline
Scan type	Cyclic (1 scan min^{-1})	Cyclic (1 scan min^{-1})
Scan range (nm)	200–322.6	273.59–276.09
Integration time (ms)	20	20
Averaging	5	5
Total scans	40	21

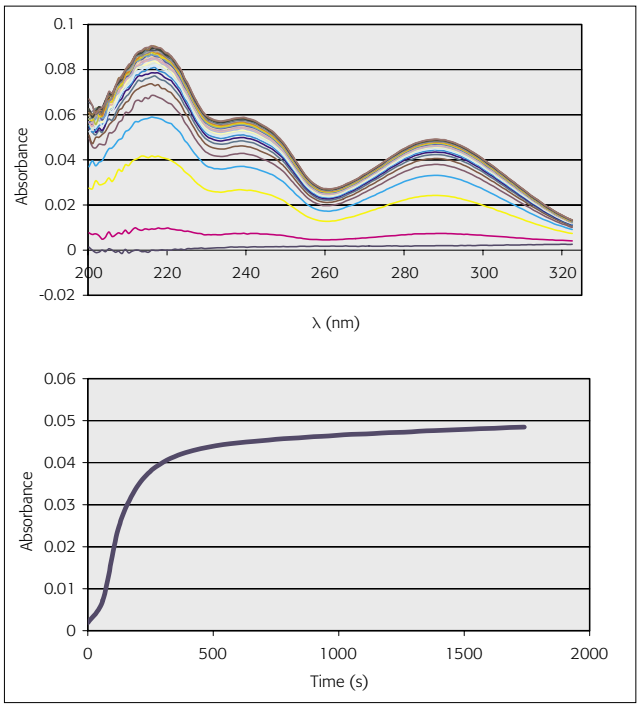


Figure 1. Top: a series of spectra collected in the range 200–322.6 nm at 60 s intervals from a suspension of form I carbamazepine in 2-propanol at 22°C. Bottom: the dissolution profile obtained by plotting a single wavelength (285 nm) versus time.

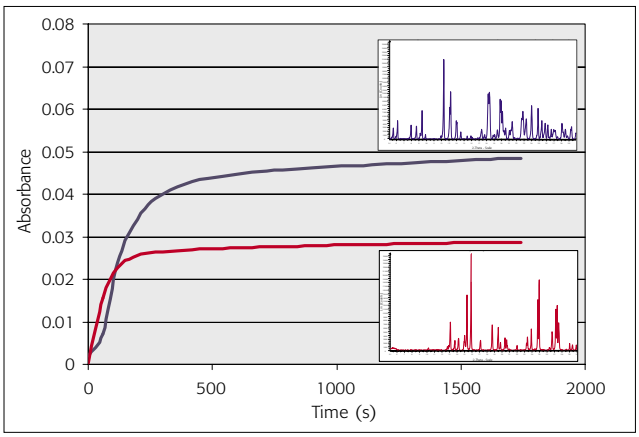


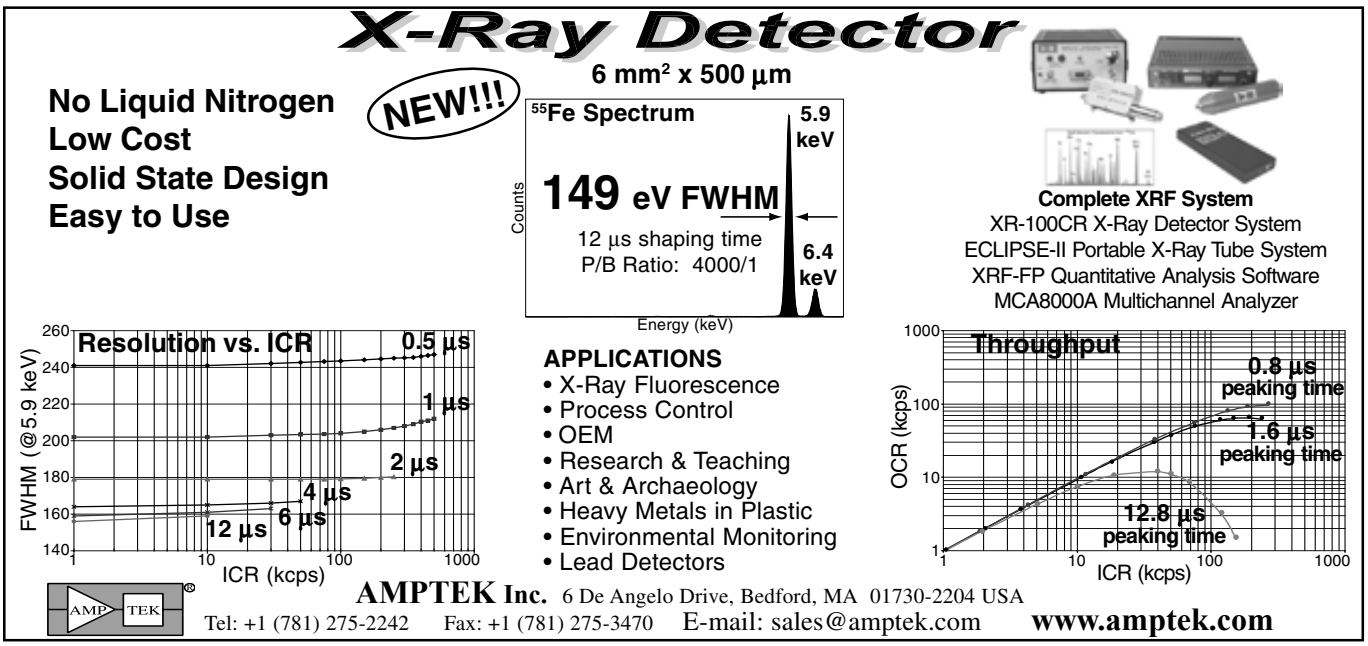
Figure 2. Powder dissolution profiles of form I (blue) and form II (red) of carbamazepine in 2-propanol at 22°C (λ_{max} 285 nm). The profiles clearly show the higher solubility and more rapid dissolution rate for form I. Inset: XRPD patterns of form I (top, blue) and form II (bottom, red) in the range 5–30° 2θ collected using Cu Kα_1 radiation, capillary geometry and linear PSD.

approaches are manpower intensive and require care to ensure filtration and dilution steps as well as temperature differences between the dissolution medium and the measurement cell do not introduce errors to the recorded values.

The data presented here were collected using a Zeiss MCS 501 UV-NIR spectrometer (deuterium CLD 500 source, 215–685 nm), equipped with a Hammamatsu photodiode array detector and Hellma ATR probe. Data collection parameters are given in Table 1.

Equilibrium solubility and dissolution measurements

The measurement of C_s and J for a powder sample is rendered straightforward by the use of *in situ* fibre optic ATR probes. The temperature of the dissolution medium is allowed to equilibrate, the spectrometer is set to record spectra at predefined time intervals over the



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duration of the experiment and the ATR probe is immersed in the dissolution medium (Table 1). Absorbance measurements commence on the addition of powder to the dissolution medium and a characteristic powder dissolution profile is obtained by plotting the absorbance at a specified wavelength over time (Figure 1). Using a calibration curve, prepared from a series of standard solutions, absorbance data can be automatically obtained in the form of concentration values. It is worth noting that, particularly when dealing with low C_s compounds, the experiment may need to run for many hours to ensure that equilibrium is reached. *J* is determined from the slope of the dissolution phase of the profile and C_s from the height of the equilibrium plateau. This approach allows the impact of various factors (including, solvent, pH, temperature, stirring rate, particle size distribution, polymorphism) on the dissolution properties of a drug to be easily characterised.

The relative equilibrium saturation solubilities of polymorphs of a pharmaceutical solid provide a reliable and convenient means of identifying the most thermodynamically favourable form, i.e. the lowest solubility form. For example, repeating the dissolution experiment under identical conditions using a sample of another polymorph, a comparison of the UV absorbance spectra shows that form II carbamazepine is more favourable than the triclinic form I at 22°C (Figure 2). Comparisons of C_s values for different forms must be carried out in the same dissolution medium (although the solubilities of polymorphs in a different solvent will yield the same solubility ratio).

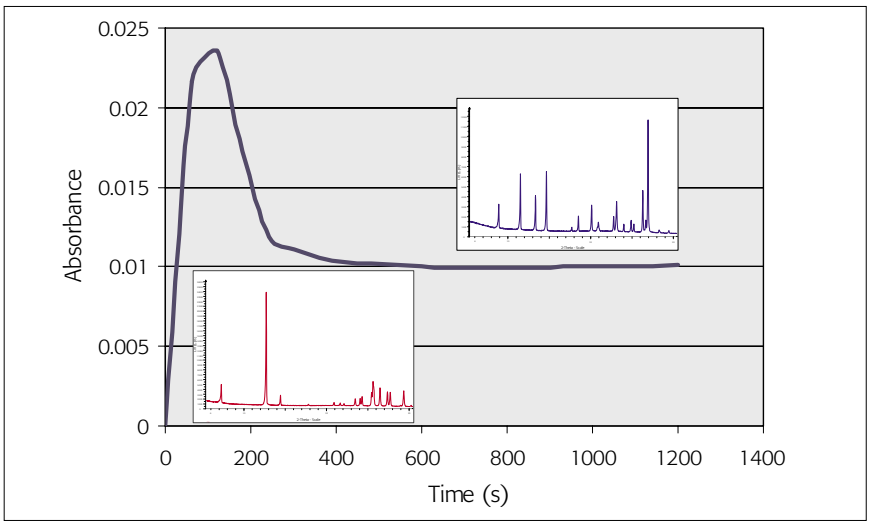

Figure 3. Powder dissolution profile for anhydrous theophylline in water at 22°C (λ_{max} 275 nm). Inset: XRPD patterns in the range 5–30° 2θ for anhydrous theophylline (red) and theophylline monohydrate (blue) collected from the raw material and from a sample of suspended solid taken after 20 min, respectively. XRPD data were collected using Cu Kα_1 radiation, capillary geometry and linear PSD.

ATR UV dissolution experiments can also identify the occurrence of solution-mediated transformations in suspended solids under isothermal conditions. As a conversion from a metastable form to a more stable crystal structure will be accompanied by a reduction in C_s, the dissolution profile will demonstrate a characteristic fall-off from a maximum value prior to reaching equilibrium. For example, form I carbamazepine will gradually convert to the more stable form II when in contact with solution for approximately four hours. However, a benefit of the rapid data acquisition times available using this system is the ability to track transformations which occur more rapidly – over minutes rather than hours – in detail. The anhydrous form of theophylline undergoes a solution-mediated transformation in aqueous solution to form the more stable monohydrate form (Figure 3). The experimental results show the characteristic dissolution curve obtained in such cases, which for theophylline, shows complete transformation has occurred in less than 7 min. Where transformation kinetics are relatively fast, the short cycle times between measurements allow accurate estimates to be obtained for C_s of the metastable form. By withdrawing samples of the suspended solid at various time intervals throughout the transformation, X-ray powder diffraction (XRPD) can be used to confirm the structural transformation in the suspended solid. Moreover, where unknown forms are encountered, XRPD can be used to determine lattice parameters, space group and crystal structure of the emergent polycrystalline phase, without the need to grow single crystal samples.

When combined with accurate control of the temperature of the dissolution medium, measurements of C_s as a function of temperature can be used to provide information on the relationship between different physical forms, for example to identify changes in the relative thermodynamic favourabilities of polymorphs within a specific temperature range. Ideally, the data acquisition and temperature control systems should be integrated to afford complete automation of sample environment and

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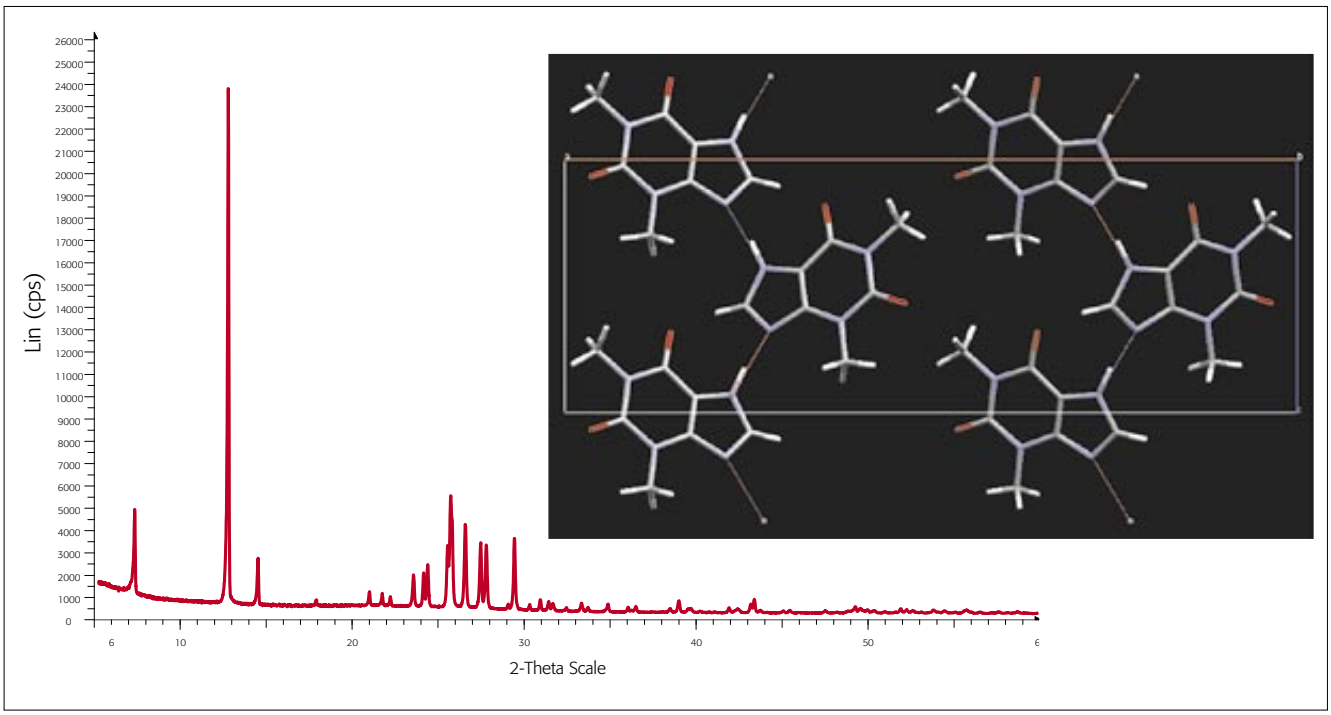

Figure 4. Capillary XRPD data (left) collected from a sample of anhydrous theophylline in the range 5–70° 2θ (*ca* 1.3Å resolution). The crystal structure (right, viewed down the *b* axis) was determined using the simulated annealing approach embodied within the DASH structure determination package. The best structure returned from 20 simulated annealing runs yielded a profile χ^2 / Pawley χ^2 ratio of 1.9 confirming the structure as solved. Molecules crystallise in space group *Pna* 2_1 with lattice parameters, a=24.566Å, b=3.825Å, c=8.481Å. Dashed lines indicate hydrogen bonded intermolecular contacts within the structure.

data collection. It should also be noted, however, where quantitative C_s values are required, temperature and concentration must be included in the calibration series to account for background absorbance changes in the dissolution medium across the values of interest.

Conclusions

In the context of physical form characterisation, the required instrumental specification balances the need for minimum sample preparation and data acquisition time, and the ability to deal with both weak and strongly absorbing compounds across a wide range of concentrations. The ability to integrate the instrumental control with software controlling the temperature of the dissolution medium is also highly desirable. The principal benefit of the use of an ATR probe is in affording the ability to accurately measure UV/vis absorbance in the presence of suspended particles, without the need to carry out time-consuming manual sampling, filtration and dilution steps or to remove the sample from the temperature controlled dissolution environment. The rapid data acquisition rates afforded by automated *in situ* approaches such as ATR UV spectroscopy are vital for detecting rapid changes in solubility resulting from structural transformations.

These data can help to complete the picture of the thermodynamic relationships between physical forms of pharmaceuticals: a prerequisite for understanding polymorphism in organic solids. This extends the utility of dissolution experiments beyond simple routine measurements of individual parameters and allows researchers to exploit the automated data acquisition afforded by modern instruments and maximise the efficiency with which polymorphic materials are characterised.

Further reading

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