Investigating drug-polymer interactions using optical DSC

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Thermometric analysis techniques provide pharmaceutical researchers vital tools to characterise, understand, and develop new drugs and drug delivery systems. Here, researchers show how optical Differential Scanning Calorimetry (DSC) analysis using an innovative technique called Thermal Analysis by Structural Characterisation (TASC) complements and enhances thermal analysis by providing more data on phase transitions. In this work, the thermal properties of several drug-polymer-excipient systems are observed and compared using DSC and TASC.

Keywords: Thermal Microscopy, DSC, Structural Analysis, Pharmaceuticals, Polymers

In the pharmaceutical industry, it is common to incorporate drug compounds into a polymer matrix to address some of the complications of working with active chemicals. These include preparation of amorphous solid dispersions for the delivery of poorly soluble drugs, development of film forming systems for topical drug delivery [1], development of adhesive transdermal patches, drug-containing coatings of biomedical devices and novel 3D printed dosage forms. To that end, gaining an understanding of drug-polymer miscibility is important for pharmaceutical applications.

DSC is the most common method used to understand the behaviour of drug-polymer mixtures. This technique has been an extremely useful characterisation tool and has a range of methodologies which can be implemented for pharmaceutical analysis, specifically for drug-polymer interactions. Analytical capabilities include observing drug melting point depression, melting enthalpy analysis, and polymer glass transition temperature analysis [2]. However, there are challenges brought about by using DSC to study these interactions, which include the time-consuming nature of the experimental work and difficulties with detection of the interaction of compounds. Sometimes DSC can not be used if the polymeric material contains other excipients e.g. plasticisers or chemical penetration enhancers.

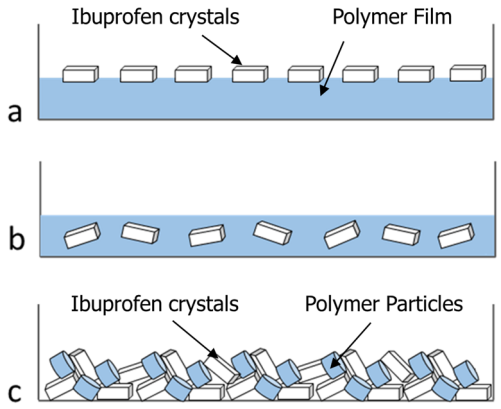


Figure 1. Different schematic illustrations of the experimental setups used to study drug polymer interaction by optical DSC, (a) ibuprofen crystals placed on top of a polymeric film solvent cast into the DSC pan, (b) ibuprofen crystallised out within a polymeric film solvent cast into the DSC pan and (c) the physical mixture of ibuprofen and polymer particles.

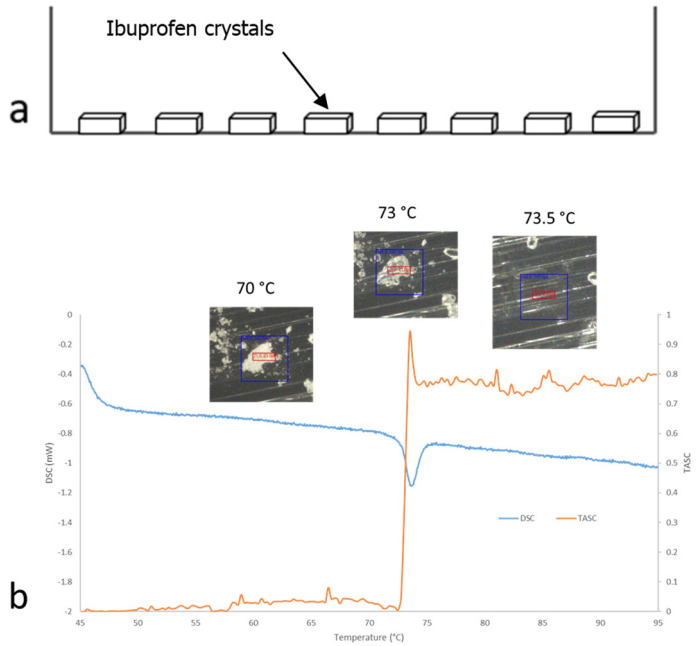


Figure 2. Optical DSC of ibuprofen, (a) shows a schematic illustration of the experimental set up, (b) shows the DSC thermogram and associated TASC output from the area identified in red in the selected optical images.

In this work, we look to address some of the shortcomings of traditional DSC for pharmaceutical analysis by using a thermo-optical sample analysis system. Here, results are presented from sample analysis using a system comprising Linkam's Optical DSC450 and Imaging Station alongside the Thermal Analysis by Structural Characterisation (TASC) software, which uses optical analysis to track structural changes in the sample as a function of temperature.

To explore the practicality of the DSC450 to examine drug-polymer interactions, we chose to investigate the effect of combining polymers and excipients with the anti-inflammatory drug ibuprofen. The ibuprofen (99.9% grade) was supplied by Sequoia Research Products Ltd. (Pangbourne, UK). We initially trialled three experimental setups shown in **Figure 1**. These were: (a) ibuprofen crystals placed on top of a polymeric film which was solvent cast into the DSC pan, (b)

crystalline ibuprofen within a polymeric film solvent cast into the DSC pan, and (c) the physical mixture of ibuprofen and polymer particles.

Following initial experimental testing of these three configurations, the method of placing 0.1mg ibuprofen crystals on top of a polymeric film solvent cast into the DSC pan (**Figure 1a**) was identified to be the most suitable methodology for understanding drug-polymer interactions. Configuration (a) has been published previously for TASC [3], while configurations (b & c) are more common for conventional DSC. The main advantage of using (a) is that you can easily set the experiment up so that you can see the drug crystals and how they change. With the other setups it is more difficult to focus on individual crystals and to know what they are in contact with. One notable point with configuration (a) is that it necessitates use of a relatively low sample mass of the drug, so the melting enthalpy peaks are small. This may pose problems for particularly subtle peaks, but also enables research with small sample quantities.

Firstly, to characterise the behaviour of pure ibuprofen on its own, a control experiment was carried out using pure ibuprofen crystals as shown in **Figure 2a**. The sample was analysed with the DSC450 in a temperature range of 45-95°C at a rate of 5°C per minute. Meanwhile, images were captured of the sample using a Linkam Imaging Station and camera setup, recording images at a rate of 10 frames per second. The image sequence was used to perform TASC analysis in LINK software, in which the structural changes are characterised and output as shown in **Figure 2b**. As seen in the graph, the melting of ibuprofen occurs at approximately 74 °C, and the melting point identified by TASC corresponds with that measured by DSC.

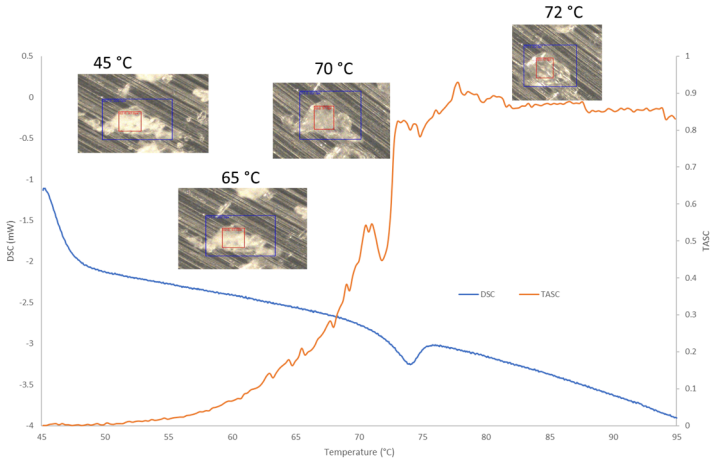


Figure 3. Optical DSC of ibuprofen on top of a solvent cast film of Eudragit RS showing the DSC thermogram and the associated TASC output.

Following the initial test, the next stage was to examine the effect of the presence of a polymeric film on the melting transition. The first polymer tested was Eudragit ® RS (EuRS), supplied by Evonik Ltd, which is a commercial pharmaceutical grade polymer commonly used for oral drug delivery for delayed or sustained release, as well as for film-forming systems such as application to skin [2]. The films were prepared by casting 30 micro litres of polymer solution in the pans. The mass of polymer in the pan was approx. 1-1.5 mg and the drug mass was approx. 0.1 mg.

The polymer was placed in the DSC pan and allowed to dry, before the ibuprofen crystals were placed on top of the film. The sample was tested following the same procedure as for pure ibuprofen, and the results are shown in **Figure 3**. In this case, when ibuprofen is placed on top of the EuRS film, the melting point occurs at the same temperature, but there appears to be a depression in the DSC trace i.e. the melting point is less pronounced. However, TASC identifies structural changes starting at a lower temperature, approximately 55 °C. The images associated with the TASC output show that interaction between the drug and the polymer occurs at temperatures below where there is a DSC signal, as evidenced by the decreasing opacity of the ibuprofen crystals. This indicates that TASC has greater sensitivity for studying drug polymer interactions.

Often within pharmaceutically relevant polymeric systems, other excipients are present as well as the drug and polymer. Typically, it is the behaviour of the drug in this mixed carrier that is most relevant to understanding the pharmaceutical properties of the formulation or device. In film-forming systems for topical drug delivery, such excipients include chemical penetration enhancers such as propylene glycol and can also act as plasticisers.

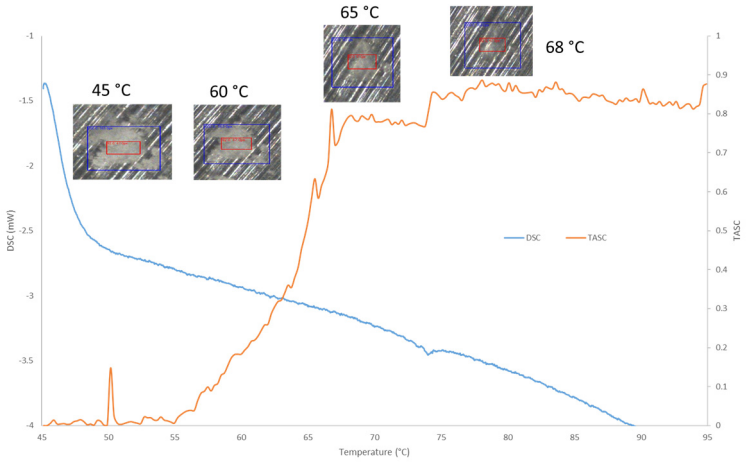


Figure 4. Optical DSC of ibuprofen on top of a solvent cast film of Eudragit RS containing propylene glycol showing the DSC thermogram and the associated TASC output.

Previously, understanding drug miscibility in such pharmaceutically relevant systems using DSC has been extremely challenging.

Figure 4 shows the optical DSC data for one such drug-polymer-excipient system, a film containing EuRS with propylene glycol. From the DSC trace, it is difficult to discern any specific phase transition, with small changes throughout the trace obscuring the known melting point of ibuprofen. However, the TASC trace is clearer, showing the decreasing opacity of the ibuprofen crystals, with a shift in the trace at approximately 74°C. The change in the TASC signal starts at approximately the same temperature as with the EuRS film (**Figure 3**) however the gradient is much steeper, demonstrating a stronger interaction with the polymeric film containing propylene glycol.

Next, the same procedure was repeated using another film-forming polymer, Eudragit E (EuE), which is commonly used in pharmaceutical compounds as a coating material. The optical DSC data from ibuprofen crystals on top of a solvent cast polymer film of

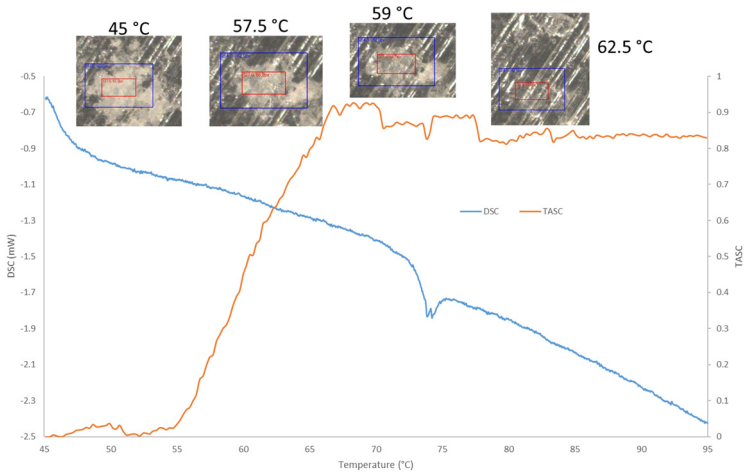
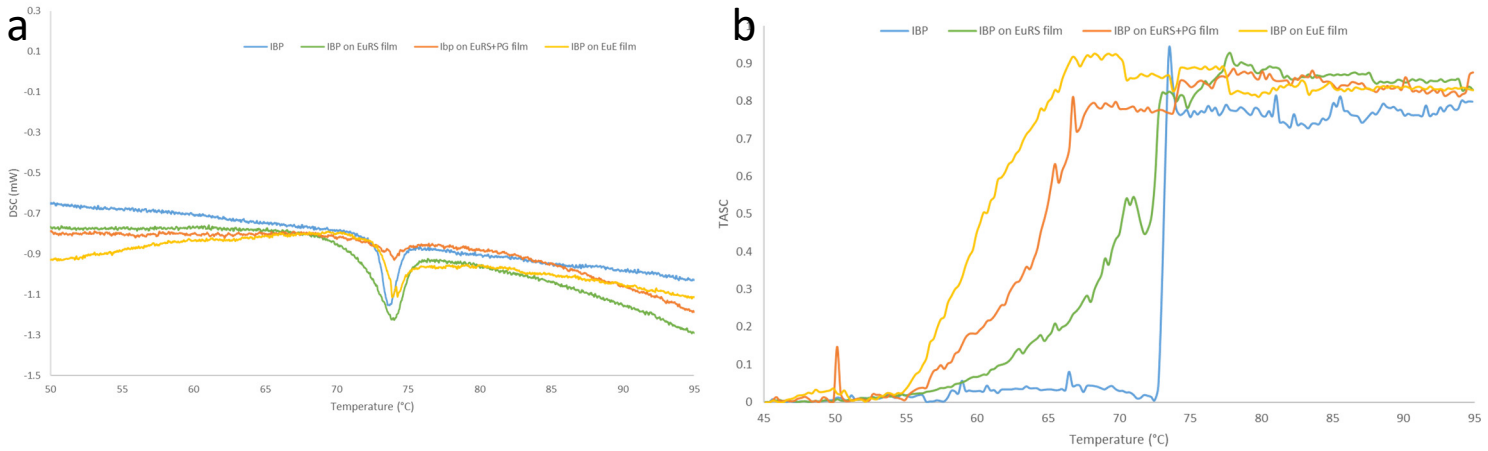


Figure 5. Optical DSC of ibuprofen on top of a solvent cast film of Eudragit E showing the DSC thermogram and the associated TASC output.



Figures. Graphs showing the DSC thermograms (a) and the associated TASC outputs (b) from each of the sample materials, highlighting the sensitivity of each technique around the phase transition temperature.

EuE is shown in **Figure 5**. Here, the melting of ibuprofen can be discerned from the DSC trace, however the enthalpy is small which gives the 'noisy' melting peak. Conversely, the TASC output is clear, reflecting the decreasing opacity of the ibuprofen crystals in the optical images and identifying the phase change. The change in the TASC signal starts at approximately the same temperature as with the EuRS film (55 °C), however the gradient is much steeper, demonstrating a stronger interaction with EuE.

To show the value of TASC in aiding understanding of these interactions, the TASC outputs and DSC outputs of the above data are overlaid in **Figure 6a** and **b**. Comparison of the outputs from these two analysis systems demonstrates the potential of using the optical DSC to study interactions between drugs and polymers, with TASC providing extra information to enhance the clarity and understanding of the conventional DSC. In some cases, for example ibuprofen with EuRS, a clear melting point depression can be seen similar to what has been published previously[4,5]. For the other two polymeric films, using the DSC alone it is difficult to interpret the changes in the DSC thermogram, and establishing what could be done to understand any interactions in these systems would require considerably more experimentation utilising for example utilising different heating rates or different experimental set ups. In comparison, using TASC in combination with DSC allows a fuller understanding of the interaction between the polymer, and the TASC curve has more sensitive transitions that begin to occur before those seen with DSC, adding supplementary data which enables the phase transitions to be better interpreted. For example, for ibuprofen with EuRS with propylene glycol, TASC indicates ibuprofen melting point depression / dissolution into the polymer matrix occurs at relatively low temperatures, leaving little drug present in crystalline form to provide the melting peak. Analysis of this type has not been possible previously with DSC.

In summary, we investigated the impact of two pharmaceutical polymers and one excipient on the melting point of the anti-inflammatory drug ibuprofen. We found the melting point of ibuprofen to be around 74°C which is in line with other findings. When combined with the polymers, we found both polymers (EuRS and Eudragit E) caused a depression in the melting point of ibuprofen. Furthermore, when the excipient propylene glycol was used, the sensitive optical technique TASC was able to reveal structural changes in the compounds beginning at around 55°C, showing dissolution of the compound begins to occur at a lower temperature than the melting of pure ibuprofen. This work shows the strength of combining traditional DSC analysis with an optical structural characterisation technique such as TASC. A further benefit is the ability to obtain accurate results with low mass samples.

References

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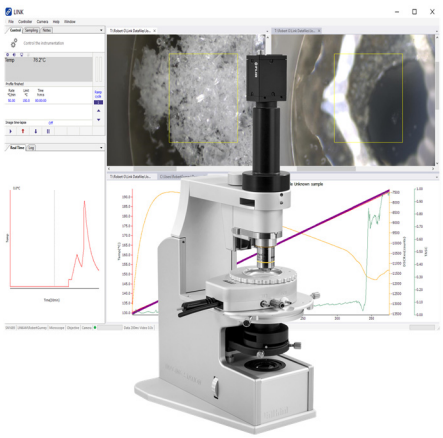

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