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A discriminatory intrinsic dissolution study using UV area imaging analysis to gain additional insights into the dissolution behaviour of active pharmaceutical ingredients

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ABSTRACT

For efficient and effective drug development it is desirable to acquire a deep understanding of the dissolution behaviour of potential candidate drugs and their physical forms as early as possible and with the limited amounts of material that are available at that time. Using 3–10 mg sample quantities, the ability of a UV imaging system is investigated to provide deep mechanistic insight into the intrinsic dissolution profiling of a range of compounds and physical forms assessed under flow conditions. Physical forms of indomethacin, theophylline and ibuprofen were compressed and their solid-state form confirmed before and after compression with X-ray methods and/or Raman spectroscopy. Intrinsic dissolution rates (IDRs) were determined using the compact's UV-imaging profile. The ratio in the IDRs for theophylline anhydrate over hydrate was 2.1 and the ratio for the alpha form of indomethacin over the gamma form was approximately 1.7. The discriminatory power of the novel UV area visualisation approach was shown to be high in that process-induced solid-state dissolution differences post-micronisation could be detected. Additionally, the scale-down system was able to visualise a previously observed increase in ibuprofen IDR with an increase in concentration of sodium dodecyl sulphate. The mechanistic dissolution insights from the visualisation approach are evident.

1. Introduction

Within the pharmaceutical industry there is a continuing drive to reduce the timescale and cost of progressing lead candidate drug molecules through to a finished dosage form. However, in addition to this, the advent of high throughput screening and combinatorial chemistry over the last three decades has also increased the number of potential new chemical entities that now need to be considered. Given these competing demands, the decision of which new chemical entity to progress is often now determined much earlier in the development pathway, where often only very limited quantities of API less than 1 g is available. Previously the solubility of a compound was often the key property to determine the lead candidate. However, given the more common trend of new candidate molecules to be poorly soluble, falling into the BCS class II or class IV (Lipinski et al., 1997; Ku, 2008) an increased understanding of their dissolution behaviour is necessary to aid the development of a drug candidate.

The physico-chemical data used and the approach to select a suitable lead candidate varies only slightly between pharmaceutical companies (Lipinski et al., 1997; Balbach and Korn, 2004) but all tend to be based around understanding the key issues of permeability, solubility, stability and desired dosage form. Given there is normally only limited quantities of material available at this stage several assumptions and calculations are often used in combination with high throughput experimental techniques to select the lead candidate. One area where these high throughput techniques are employed is in the field of polymorph and salt screening. Here milligram quantities of several different polymorphs, pseudo-polymorphs and salts are produced that require evaluation.

We have focussed upon one key area when evaluating each possible form, namely that of the dissolution rate of the compound. In the case of poorly soluble compounds the design of new dosage forms can, and often is, guided by dissolution rates (Baxter et al., 2005). Despite this there are numerous challenges still facing dissolution testing, not least the limited sample amounts available during early stage development. Inconsistent dissolution data can often be produced from a number of factors (Cox and Furman, 1982; Kamba et al., 2003; Moore et al., 1995; Qureshi and Shabnam, 2001; Son and McConville, 2009). One such factor that is worthy of attention is that of the surface area of the powder samples and the influence this can impart on observed dissolution behaviour. This, of course, is something not easily overcome when dealing with very limited sample quantities and number of batches.

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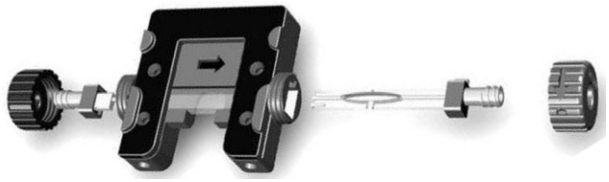

Fig. 1. Schematic of SDI300 cartridge.

Traditional methods to determine the intrinsic dissolution rate of a compound (Wood apparatus or USP II apparatus in combination with a pellet holder) (United States Pharmacopeia) are available. These eliminate the influence that differing surface areas have on dissolution behaviour by compressing the powder sample to form a flat surface, of fixed diameter, that is in contact with the dissolution media. However, when it comes to early stage development, this can be an undesirable approach as it expends significant amount of valuable active pharmaceutical ingredient (API), has long sampling times and uses large volumes of dissolution media. Additionally it may also require additional analysis, for example, high performance liquid chromatography (HPLC) (Laitinen et al., 2010; Mauger et al., 2003).

Due to these constraints, alternative technologies have now been investigated (Brown et al., 2004; Marabi et al., 2008). Some Pharmacopeal commercially available flow through dissolution apparatus are available (USP IV dissolution apparatus). These have the advantage of requiring only small sample quantities. However, as with the other traditional dissolution apparatus, often additional method development is required.

The development of an UV area imaging instrument, the Actipix SDI300, has recently been used to provide insights into the diffusional properties of active pharmaceutical ingredients (Boetker et al., 2011) under static conditions. However, we have employed the laminar flow capabilities to provide an invaluable insight into both the dissolution and diffusional behaviour of a sample with its real time UV imaging analysis. This approach has several advantages in that potentially both solubility and dissolution behaviour of a compound can be measured, analysis times are rapid and often less than 10 min, only milligram quantities of sample are required and different dissolution media can be studied easily during a single experiment. It follows that the approach is suitable for the analysis and comparison of different polymorphs and salts of active pharmaceutical ingredients, in particular during lead candidate selection where only limited quantities of sample are usually available.

For the approach we present as with any intrinsic study, however, it is important to remove the influence that different particle size and surface area effects can impart on the apparent dissolution behaviour. Therefore, in order to eliminate these influences all samples were compressed to produce a compact with a flat surface with a diameter of 2 mm. The samples were then placed into a quartz cell and dissolution media is passed across the face of the sample using a syringe driver. Prior to entry to the cell the dissolution media is heated to 37 °C by passing through a heating block. Above the quartz cell the UV area imaging camera that is capable of measuring the absorbance across the entire cell is positioned. The intrinsic dissolution rate is determined within the software from the UV absorbance of the dissolution media as it passes a predetermined area in the cell. A schematic representation of the sample cartridge used for studying intrinsic dissolution rates with the SDI300 is given in Fig. 1.

Three different compounds were selected for study here. They were chosen due to their differing dissolution properties that have often proved difficult to study using traditional dissolution apparatus.

Firstly, the highly soluble compound theophylline, a biopharmaceutical classification system (BCS) I compound was selected. Theophylline is known to exist in several physical forms. The anhydrous and the monohydrate forms of theophylline have been well characterised by several authors (Ono et al., 2001; Debnath and Suryanarayanan, 2004; Phandis and Suryanarayanan, 1997). However, the tendency of anhydrous theophylline to form hydrates upon exposure to moisture makes any study of the dissolution behaviour of the anhydrous theophylline difficult. Therefore, given the rapid analysis times and continuous flow applied during these experiments, theophylline was chosen to determine if the process of conversion can be inhibited to allow for a more detailed understanding of the dissolution properties of the metastable anhydrous form.

Secondly, in order to gain additional insights into the often complex dissolution behaviour of poorly soluble compounds, two polymorphic forms of the BCS II compound indomethacin were studied. Again this compound has been well characterised previously making this an ideal candidate for comparing the dissolution properties of polymorphic forms of poorly soluble materials. The two forms studied were the metastable alpha form and the stable gamma form. (Aceves-Hernandez et al., 2009; Greco and Bogner, 2010; Hancock and Parks, 2000; Honary et al., 2007).

Thirdly, ibuprofen, another poorly soluble compound (BSC II) that has been well characterised previously (Kokot and Zmidzinska, 2001; Levis et al., 2003; Stephenson et al., 2006), was studied. Here, the common influence on apparent dissolution properties, namely differing dissolution media and addition of surfactant were studied. Finally, a comparison of the dissolution behaviour of ibuprofen free acid and sodium salt of ibuprofen was also undertaken.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (batch 048K0709), the gamma form of indomethacin (batch 61K1368), ibuprofen (batch 148839) and ibuprofen sodium salt (batch 027K2111) and sodium dodecyl sulphate (SDS) (batch 102H3522) was purchased from Sigma–Aldrich, Dorset, UK and were used as received. Water was deionised double distilled and degassed before use. Buffer components were analytical grade.

2.2. Production of theophylline monohydrate

Theophylline monohydrate was prepared by heating a saturated aqueous solution of theophylline to 60 °C for 15 min before allowing to cool to room temperature. The sample was then dried at room temperature overnight.

2.3. Production of alpha indomethacin

The alpha polymorph of indomethacin was produced by dissolving gamma indomethacin and precipitating from a saturated methanol solution with water. The sample was then allowed to dry at room temperature.

2.4. Micronisation

Micronisation of alpha indomethacin was performed using a Retsch MM200 ballmill (Retsch GmbH, Germany). Approx. 1 g was micronised at 25 Hz for 45 min.

2.5. Powder X-ray diffraction (PXRD)

Powder X-ray patterns were obtained using a Bruker D8 Difractometer. The system comprises a scintillation counter detector and a monochromator with a Cu-Kα radiation source (λ = 0.15418 nm).

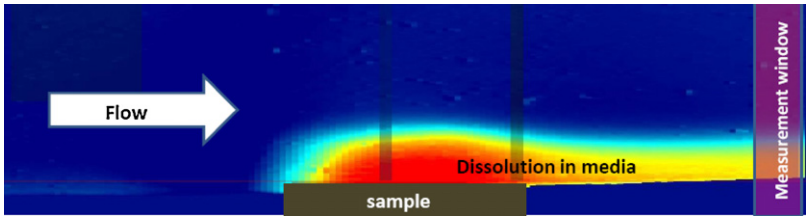

Fig. 2. Typical UV dissolution image observed from UV area imaging.

The scanning range used was between 5 and 45° of 2θ with a stepwise scanning mode using a step size of 0.05° of 2θ and a step time of 3 s. Sample rotation of 30 rpm was employed during measurements.

2.6. FT-Raman spectroscopy

Raman analysis was carried out using an FRA 106 Raman module with a Bruker IFS 66 optics system. The Nd:Yag laser operated at 1.064 μm and the scattered radiation was detected by a liquid nitrogen cooled germanium detector which gave a spectral range of 50–4000 cm^{-1}. A laser power of 900 mW with 500 scans and a resolution of 4 cm^{-1} were used.

2.7. Dynamic vapour sorption (DVS)

DVS was carried out using an IGAsorp moisture sorption analyser (Hiden Isochema Ltd., UK). The sequence of isothermal steps incorporated drying the samples to 0% RH until constant weight was achieved. The RH was then increased in increments of either 5 or 10% to a maximum of 95% RH. Samples were analysed at 25 °C.

2.8. UV imaging intrinsic dissolution

UV imaging intrinsic dissolution was performed using an SDI300 (Paraytec, York, UK). Approximately 3–10 mg of sample was compacted into sample, using a torque between 20 and 80 cNm (dependant upon sample properties) for 1 min, to create a flat surface for analysis. The sample cup was placed into a surface dissolution imaging sample holder and the dissolution media was passed across the surface of the sample at various flow rates by use of a syringe driver. As the sample dissolves in the dissolution media it is swept along the cell in the flow. Downstream of the sample, at a predetermined measurement area of the pixilated detector the UV absorbance at 280 nm was measured using the instrumental UV area imaging software. By measuring the absorbance over time in combination with the flow rate, the software is able to calculate the intrinsic dissolution behaviour of the sample. Fig. 2 shows a typical dissolution image observed by UV area imaging. Here visually, a contoured concentration map is produced that is able to give insights into both the diffusional and dissolution properties of a material.

3. Results and discussion

Whilst undertaking these studies, care was taken to ensure that only the desired form of the material was analysed. This was of particular importance, given the small sample size and sample area, when compacting the sample prior to analysis to ensure that no pressure induced surface modifications occurred under the compaction conditions used. Therefore, prior to analysis, the samples were analysed using PXRD and FT Raman spectroscopy. However, given the resultant compact pellet with a 2 mm diameter it was not easy to obtain a suitable PXRD pattern post compaction without removing the sample from its sample cup. As a result, a modified FT Raman sample holder was developed that enabled analysis of the compacted samples in situ after compaction to ensure that the surface of the material was still the desired form, as shown in Fig. 3.

Additionally, when it comes to studying the discriminatory dissolution behaviour of a material solid phase conversion can occur (Forbes et al., 1995) and any such conversion from a less stable to more stable form needs monitoring. Previous studies on theophylline report that the anhydrous form has recrystallized via a metastable hydrate to the stable monohydrate during the dissolution process (Debnath and Suryanarayanan, 2004; Phandis and Suryanarayanan, 1997). Therefore, prior to the dissolution study the metastable hydrate form of theophylline was also characterised after exposing a sample of theophylline anhydrous to moisture

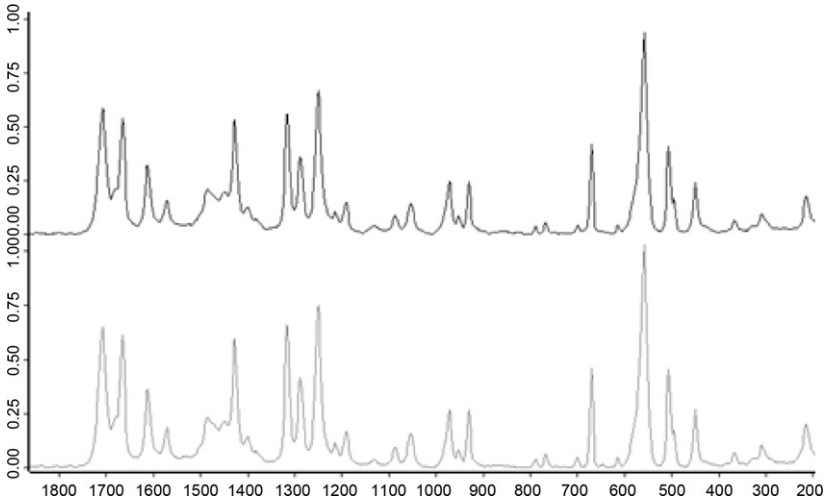

Fig. 3. Raman spectra obtained for theophylline anhydrous pre compaction (top) and post compaction (bottom).

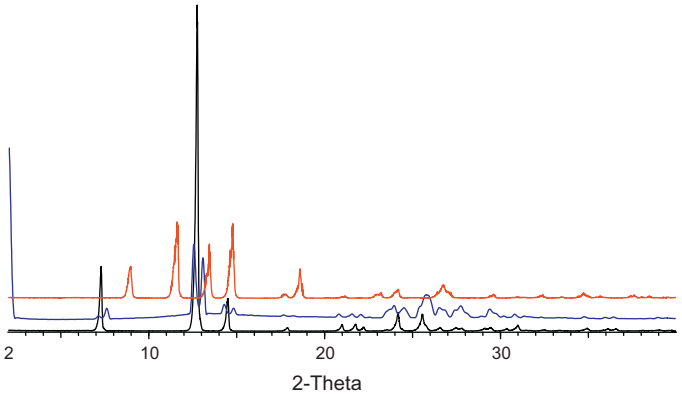

Fig. 4. Comparison of PXRD patterns of theophylline anhydrate (bottom), theophylline monohydrate (top) and theophylline anhydrate post DVS analysis (middle).

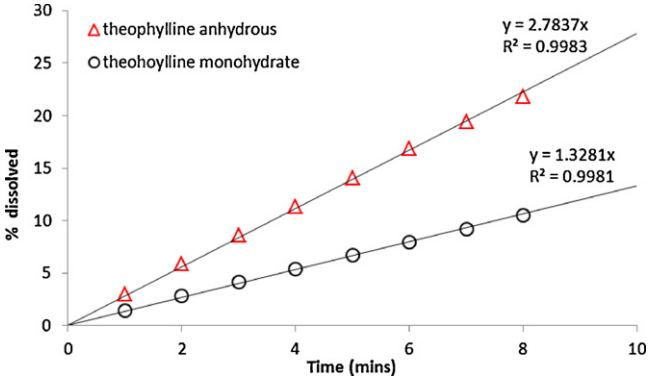

Fig. 6. Dissolution profiles for theophylline monohydrate (bottom) and theophylline anhydrous (top).

by use of dynamic vapour sorption (DVS). A comparison of the PXRD patterns observed for the anhydrous, hydrate and post DVS theophylline is shown in Fig. 4. This shows that the PXRD pattern obtained from the post DVS sample differs from the monohydrate form and is consistent with the formation of a metastable hydrate as reported previously (Phandis and Suryanarayanan, 1997).

With reference solid phase data shown in Fig. 4, the intrinsic dissolution behaviour of the two forms of theophylline could now confidently be studied here. The comparison of the intrinsic dissolution rates (IDR) obtained by UV area imaging in triplicate for the anhydrous and monohydrate forms of theophylline are shown in Fig. 5.

It must also be noted that the comparison and analysis shown in Fig. 5 is only given after 3 min dissolution time. This was to allow any non-compacted surface powder that may still be present given the low compaction force applied to be removed prior to the detailed analysis. This was necessary in this case to eliminate erroneous results due to particulates, as unlike other conventional flow through dissolution apparatus no filtering of the sample or off-line measurement is performed. From the IDR values the resultant dissolution profiles for the anhydrous and monohydrate forms of theophylline can be generated as shown in Fig. 6.

Figs. 5 and 6 show stable dissolution profiles in both forms of theophylline, with the anhydrous form having an intrinsic dissolution rate approximately 2.1 times greater than monohydrate form. A comparison of the intrinsic dissolution profiles for the two forms shown in Fig. 6 compared that using rotating disc reported by Ono et al. (2001) show similar trends in the initial dissolution profiles with the anhydrous form having an increased dissolution rate over the monohydrate. The same authors report the presence of a non-linear region in the intrinsic dissolution of the anhydrous theophylline indicating the conversion from anhydrous to monohydrate theophylline. This conversion of the anhydrous form to the monohydrate form is not observed in our experiments and may be due to the differing hydrodynamics thus inhibiting the kinetics of conversion to a hydrated form. Raman analysis of the compact post dissolution also showed no conversion to the hydrated form had occurred on the surface (data not shown).

Indomethacin is known to exist in at least two polymorphic forms: a thermodynamically stable gamma form and a metastable alpha form. A comparison of the intrinsic dissolution rates obtained in triplicate for the alpha and gamma forms of indomethacin is given in Fig. 7. It can be seen that, despite small differences between the IDR values obtained in duplicate for the alpha indomethacin, clear discriminatory differences in the intrinsic dissolution profiles of the two forms exist. The relative dissolution rates observed for the alpha form of indomethacin was found to be approximately 1.7 times greater than that of the more stable gamma polymorph. This again was expected and correlates well with that reported in literature (Aceves-Hernandez et al., 2009).

Process-induced change in the properties of a material is an important area to study (Chikhalia et al., 2006) including dissolution rate. Samples of both the gamma and alpha forms of indomethacin were micronised and their intrinsic dissolution behaviour determined from the imager. No change in physical form or detectable increase in amorphous content was observed for the micronised material to that of the non micronised material feed material, as shown in Fig. 8 by the PXRD patterns for the alpha indomethacin starting material compared to that of the micronised material.

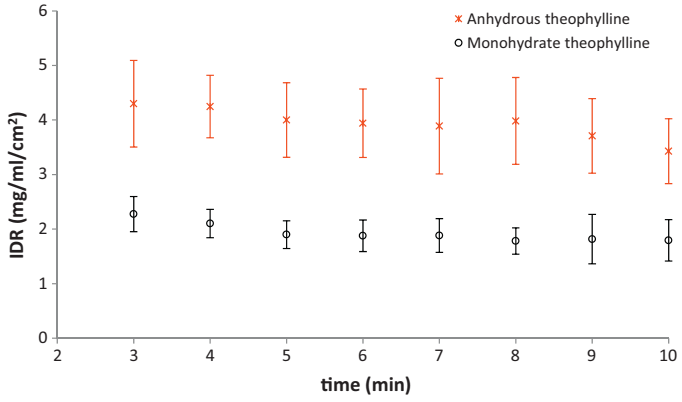

Fig. 5. Intrinsic dissolution rates for theophylline monohydrate (bottom) and anhydrate (top).

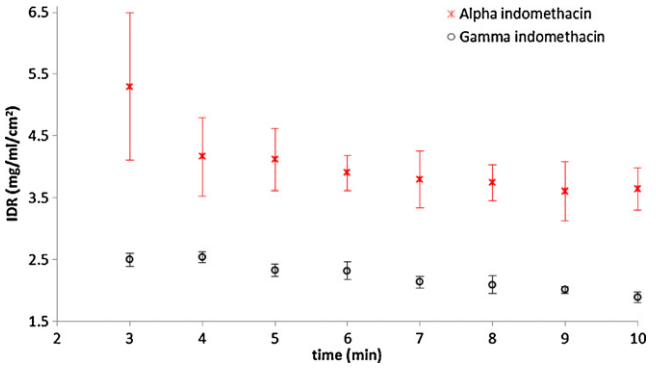

Fig. 7. Intrinsic dissolution rates for alpha (top) and gamma indomethacin (bottom).

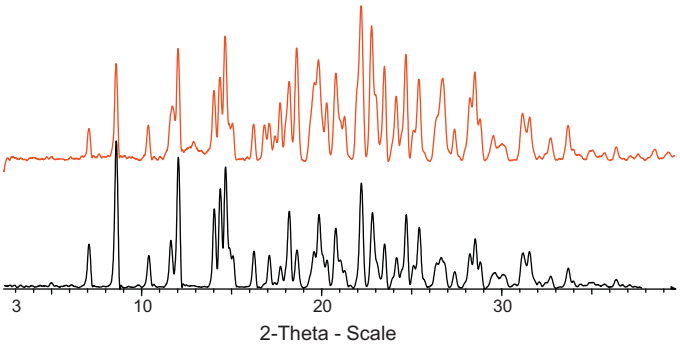

Fig. 8. PXRD of alpha indomethacin starting material (bottom) and post micronisation (top).

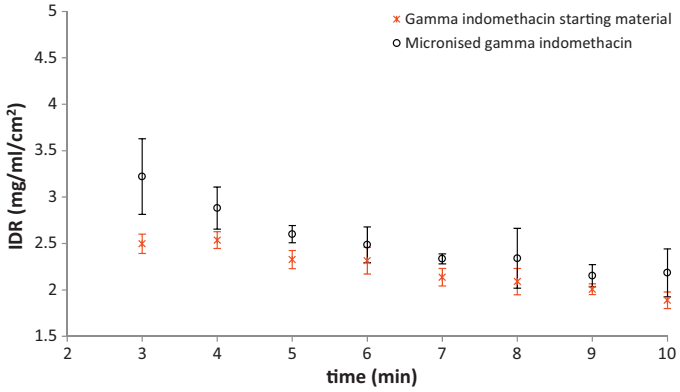

Fig. 9. Intrinsic dissolution rates for gamma indomethacin starting material and micronised gamma indomethacin.

Triplicate analysis of both the micronised and starting material of intrinsic dissolution rates of gamma indomethacin are given in Fig. 9. The majority of the points show no difference in the dissolution profiles between the micronised and starting material. This finding indicates that size reduction of this form by our method of micronisation produced no significant effect on IDR.

However, a comparison of the intrinsic dissolution rates of the micronised alpha indomethacin and starting material showed that, surprisingly, the micronised indomethacin has a much lower dissolution rate than the un-milled initial material as shown in Fig. 10. This suggests that the observed results are due to the micronisation process altering the total surface energy of the sample and relative surface chemistry. A simple model of this is to equate this change to an increase in the proportion of hydrophobic surface domains exposed after micronisation. The ability to not only discriminate

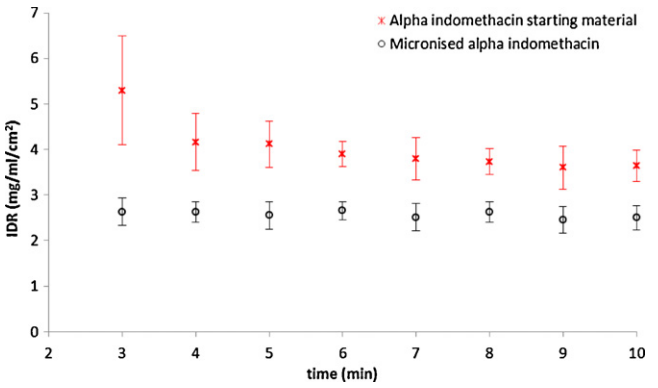

Fig. 10. Intrinsic dissolution rates for alpha indomethacin starting material and micronised alpha indomethacin.

the dissolution rates between different physical forms of a material, but also the surface morphology of the same sample after processing is of utmost importance for any understanding and optimising the dissolution properties of poorly soluble active pharmaceutical ingredients.

Given the need for an understanding of the dissolution properties of poorly soluble active pharmaceutical ingredients it is only of limited use to only study the dissolution properties of a material in one media. Therefore, the dissolution behaviour of ibuprofen in contact with differing bio-relevant media was also studied. The use of the UV area imaging clearly shows that there was only very limited dissolution of ibuprofen in a PBS buffer (pH 7.2) occurring under flow, as shown in Fig. 11A. Fig. 11B shows the visual image obtained after 10 min of continuous flow, followed by 5 min of static conditions. Here, insights into the limited diffusional properties of the material can also be studied (Boetker et al., 2011). By changing the dissolution media, the dissolution properties of the ibuprofen in differing bio-relevant media were also able to be studied.

Salt forms are classically used to alter dissolution rate. Here we have compared the dissolution behaviour of ibuprofen to that of a crystalline sodium salt of ibuprofen. Again the UV imaging snapshot, shown in Fig. 12, readily shows a much improved dissolution behaviour of ibuprofen as its sodium salt. It can be seen that a comparison of absorbance maps under flow of ibuprofen (Fig. 11A) and that obtained for the sodium salt of ibuprofen (Fig. 12) clearly indicates a lower intrinsic dissolution and diffusion into solution of the ibuprofen to that of the sodium salt. This is visualised by the reduced absorbance intensity profile of the ibuprofen.

A comparison of the measured dissolution profiles of the ibuprofen sodium salt compared to that of the ibuprofen in PBS confirms this observation and is given in Fig. 13. Here it can be seen that a

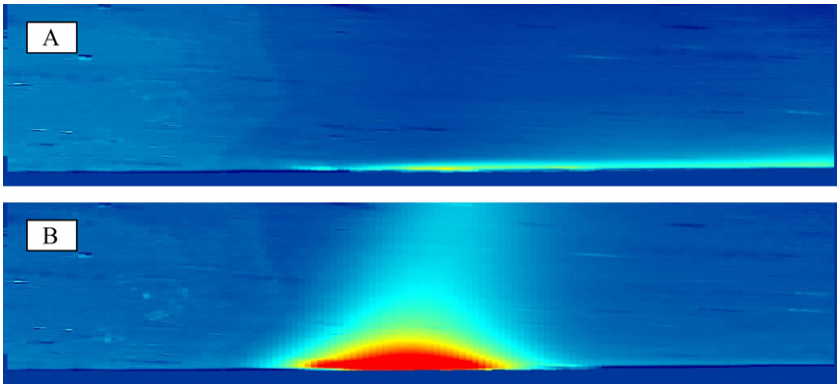

Fig. 11. (A) UV area image of ibuprofen under continuous flow and (B) UV area image after 10 min of continuous flow followed by 5 min of static conditions.

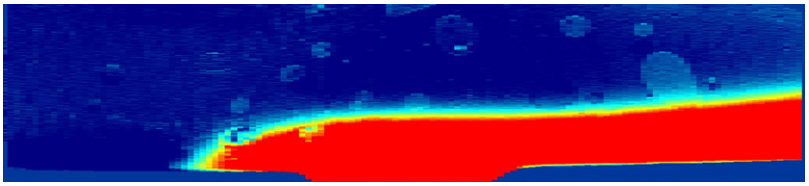

Fig. 12. UV area image of ibuprofen sodium under continuous flow.

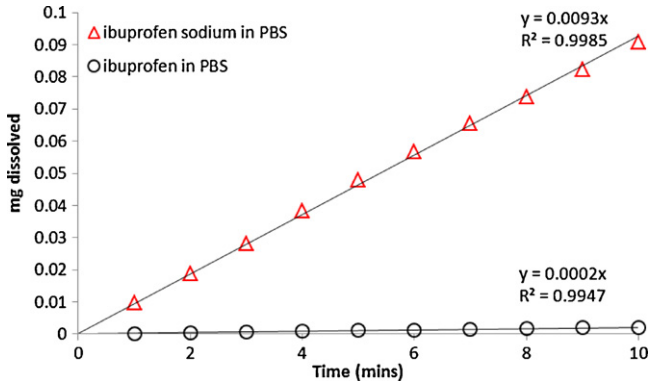

Fig. 13. Comparison of the dissolution profiles of ibuprofen acid (bottom) and ibuprofen sodium (top).

46.5 fold increase in the dissolution rate of sodium salt compared to the ibuprofen is observed.

Often when performing any dissolution study on poorly soluble, hydrophobic material, a surfactant wetting agent is applied to enhance the dissolution properties of a material for discriminatory analysis. However, as shown in this paper the use of UV area imaging is a very sensitive technique and is able to discriminate the dissolution properties of differing materials without the need for added surfactant. However, to help gain an insight into the effect of addition of a wetting agent that can impart on the dissolution behaviour of a compound PBS buffers (pH 7.2) were prepared that also contained 0.02 M SDS (below the CMC) and 0.08 M SDS (above the CMC). The dissolution profiles of ibuprofen acid in these two media were also compared.

Fig. 14 shows comparative dissolution results where the addition of SDS at 0.02 M (below the CMC) brings about an enhanced two fold dissolution rate increase than that observed in its absence. The addition of 0.08 M SDS (above CMC) to the running media buffer shows a 3.5 fold increase in dissolution rate compared to that obtained without SDS. Our scale-down data obtained under flow conditions is consistent with that previously reported by a different method (Bhattamishra and Padhy, 2009) and is supportive of their observation that the improvement in dissolution by the addition of SDS is aided not only by wetting the ibuprofen but also by the incorporation of ibuprofen into a micelle core (Stephenson et al., 2006; Bhattamishra and Padhy, 2009). Whilst an understanding of the effects of surfactant concentration may be important when identifying formulation excipients that may improve solubility and bioavailability, we demonstrate that a wetting agent is not required for discriminatory dissolution studies by this technique and that there is a need for caution when trying to understand and compare the dissolution behaviour of different species if additional wetting agents are used (Bhattamishra and Padhy, 2009).

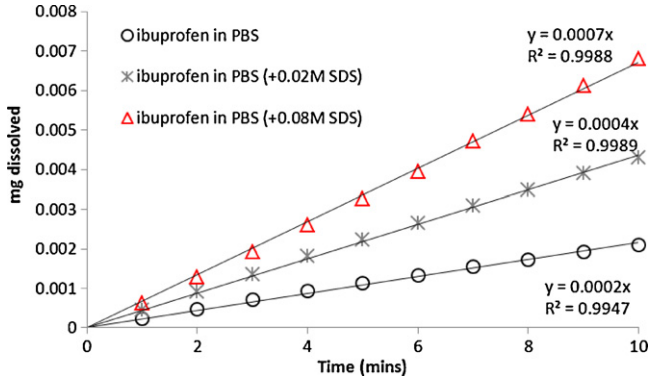

Fig. 14. Dissolution profile of ibuprofen in PBS with differing concentrations of SDS wetting agent.

4. Conclusions

A thorough understanding of the dissolution properties of a material and its differing polymorphic/salt forms is required when evaluating pharmaceutical compounds to progress to product development. In this paper we have focussed upon the use of a UV-imaging flow-through dissolution instrument to determine the dissolution properties of various samples of theophylline, indomethacin and ibuprofen. Our findings suggest that by using small sample quantities of between 3 mg and 10 mg intrinsic dissolution rates can be measured repeatably and reproducibly to discriminate between polymorphic and salt forms and dissolution media effects (utilising small volumes) with the potential to provide mechanistic insights including the effect of processing (e.g. milling) on dissolution behaviour. The ability to visually capture UV dissolution behaviour with rapid and continual measurements during flow may also help minimise the risk of erroneous findings caused by in situ conversions.

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