Application note 417/18

Combining the Pion SDi2 and Raman spectroscopy to study the dissolution and stability of diclofenac sodium salt

Background

Salt formation is often used to improve solubility of acidic drugs at low pH. When studying the dissolution of acidic active pharmaceutical ingredient (API) salt forms, results are often hard to interpret using a single technique due to their varying stability and eventual solid form conversion. Raman spectroscopy has been used in parallel with the Pion SDi2 to study the real-time surface dissolution of compacted diclofenac Na and monitor an associated solvent-mediated form transition.

Experimental

Triplicate dissolution experiments were carried out using the SDi2 (Pion Inc.) fitted with a PhAT probe (Kaiser Optical Systems Inc., Figure 1). Diclofenac Na (5 mg) was compacted in the sample holder (3 mm ID) using a 100 kg load for 60 s. The SDi2 compact flow cell was used to measure the intrinsic dissolution rate (IDR) over 40 min in 0.01 M HCl using a flow rate of 0.72 mL/min (equivalent to 2 cm/min linear velocity).

The flow cell was illuminated using alternate pulsing of 520 and 255 nm LEDs and the Actipix™ detector recorded the light intensity passing through the flow cell. These data were used to build up high-resolution images of the dissolution process in real time. Images were converted to false colour, where iso-absorbance regions were represented by blue, green, yellow, and red in order of increasing absorbance. Dissolved drug and precipitation could be studied independently, using data from the 255 nm and 520 nm LEDs, respectively. The PhAT probe was fitted with a lens to provide a 3 mm laser spot size and placed in the SDi2 so that the beam was focussed on the diclofenac compact surface (Figure 2). Raman data were collected every minute, using a 7 s exposure time. UV/Vis absorbance and Raman data were collected in tandem and processed using the SDi2 Data Analysis and Holograms 4.1 software, respectively. Multivariate data analysis was performed using Matlab (MathWorks®).

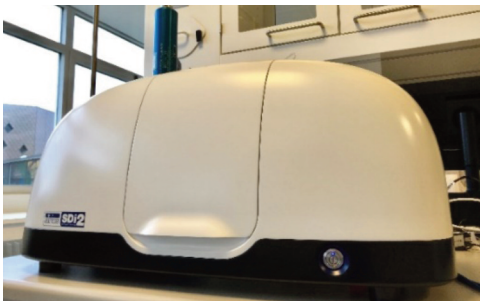

Figure 1. Photo of the SDi2 and Raman probe set-up.

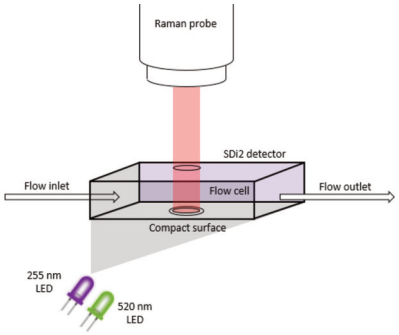

Figure 2. Schematic of the SDi2 and Raman probe set-up.

Results

IDR and cumulative mass released results obtained from the SDi2 are displayed in Figures 3 and 4, respectively. The raw data used for such measurements come from two-dimensional images of the dissolution process at the sample surface. Figure 5 depicts a selection of images from Run 3.

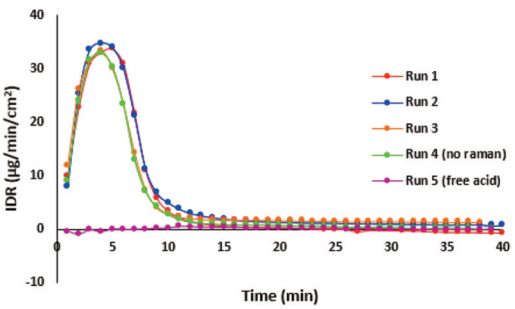

Figure 3. Diclofenac IDR versus time. Triplicate SDi2 data were collected for the sodium salt (Runs 1-3), in addition to Run 4 where the Raman probe was not active and Run 5 where the IDR of the free acid was measured.

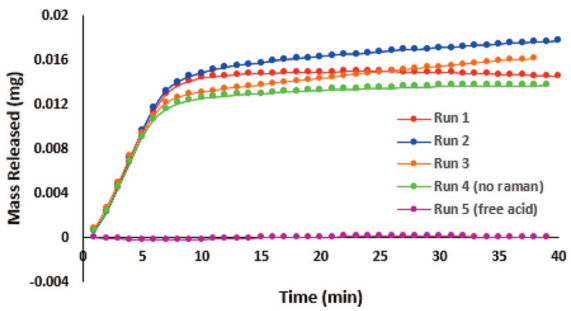

Figure 4. Cumulative amount of diclofenac released versus time. Triplicate SDi2 data were collected for the sodium salt (Runs 1-3), in addition to Run 4 where the Raman probe was not active and Run 5 where the cumulative amount of the free acid was measured.

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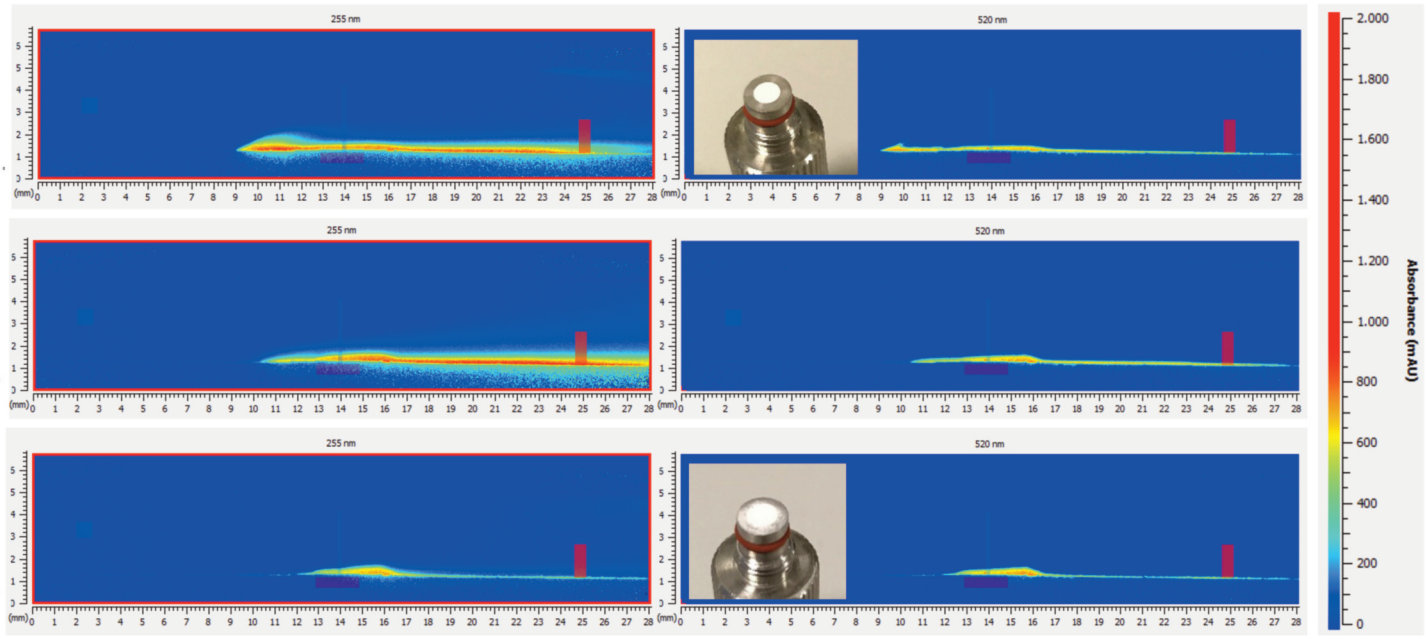

Figure 5. Still images taken from Run 3 at t=2, 6, and 10 min from top to bottom. UV (left) and visible data (right) are used to measure the IDR of diclofenac Na and monitor precipitation, respectively. Measurement zones overlay the images and were used for quantitation. The red zone towards the outlet of the cell was used to measure IDR, as described elsewhere[1]. Photos of the sample surface taken before and after the experiment are overlaid on the top and bottom images, respectively.

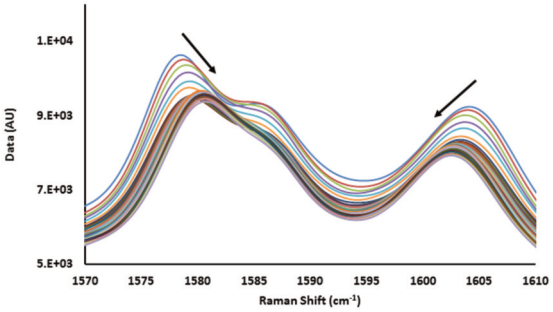

Figure 6. Superimposed partial Raman spectra for Run 1. Peak shifts were observed at 1575-1580 cm^{-1} and 1600-1605 cm^{-1}, indicative of a solid form transition. Arrows show direction of peak shifts with increasing exposure time.

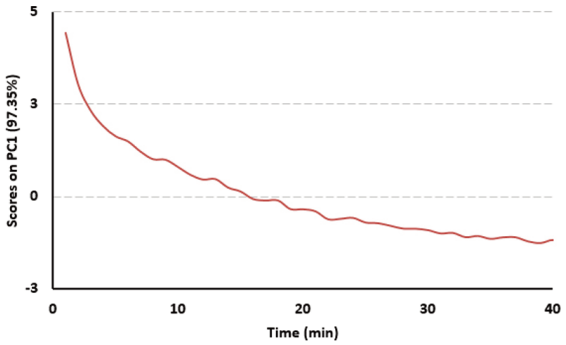

Figure 7. Multivariate data analysis (PC1 vs. time) for Raman spectra collected for Run 1. The graph provides a visual representation of the solid form transformation kinetics.

Discussion

The dissolution data are difficult to interpret from Figures 3 and 4 alone. The combination of UV/Vis imaging and Raman data provide a more complete analysis. Under the experimental conditions used, the initial IDR is relatively high but decreases to approximately zero within 15 min. SDi2 images show that the height of the compact surface increases during this time, and precipitation is visible between the surface and the cell outlet. Raman data show that the diclofenac Na rapidly converts to a different form within 5 min of exposure to acidic medium, and continues to transition at a lower rate over 40 min. This conversion of the Diclofenac Na to a less soluble form leads to precipitation and inhibits further dissolution from the compact surface. Additional experiments, such as XRPD, are required to determine the final form of diclofenac.

Conclusion

Surface dissolution imaging and Raman spectroscopy have been successfully implemented, in parallel, to study the dissolution of diclofenac Na and confirm the presence of a solvent-mediated form transition. This combination of techniques may provide useful insights during salt form selection and could be used as a valuable troubleshooting tool.

References and Funding

1) Application note "Validation of the Sirius SDi2 intrinsic dissolution rate measurement": http://www.sirius-analytical.com/resource-library/literature/sirius-sdi2-application-notes

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