Integrated UV-Vis Imaging, Light Microscopy and Raman Spectroscopy for Characterizing Piroxicam Supersaturation, Precipitation and Dissolution

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\textbf{Purpose}

The purpose of the study was to develop an integrated analytical flow-through setup for characterizing drug supersaturation, precipitation and dissolution using piroxicam as model compound.

\textbf{Methods}

A 3D printed flow-through cell with the dimensions $40.3 \times 20.8 \times 4$ mm$^3$ (l × w × d) was integrated with an Actipix D200 UV imaging system (Paraytec Ltd., York, UK) having an $11 \times 11$ mm$^2$ imaging area and two light sources (LEDs at 280 and 525 nm), a digital light microscope (Dino-Lite Premier Digital microscope, AM7013MZT) with a magnification of 40 (AnMo Electronics Corporation, Hsinchu, Taiwan). Additionally an Ocean Optics mini-UV–vis spectrophotometer (Ocean Optics B.V, Netherlands) with a flow-through cuvette recording a spectrum (200-400 nm) every 30 s was used for monitoring the effluent. A syringe pump delivered the precipitation/dissolution medium, a 0.067 M phosphate buffer, pH 7.40, at a flow rate of 1, 3, or 5 ml/min. Piroxicam (20 to 150 mg/ml) dissolved in N-methyl pyrrolidone or phosphate buffer was introduced into the flow cell via a second syringe pump at a flow rate of 5 μl/min.

\textbf{Results}

Upon injection of 5 μl 150 mg/ml piroxicam solution into the flow-through cell, piroxicam precipitation occurred almost instantaneously (Figure 1). The precipitation of solid material was detected at 525 nm whereas the absorbance measured at 280 nm was due to both dissolved and precipitated piroxicam. Local piroxicam concentrations, which were above the aqueous solubility of piroxicam at pH 7.4, were measured and found to decrease over time due to transport of drug out of the flow-through cell. The precipitated piroxicam particles were visualized by light microscopy and UV-Vis imaging. From the UV-Vis images, the size and absorbance cross section of individual particles were found to decrease over time due to dissolution. The time-dependence of the extent of precipitation as well as the cumulated amount of piroxicam dissolved were quantitatively evaluated using the imaging platform. The precipitation and dissolution properties of piroxicam as a function of drug concentration in the injected solution and flow rate were explored. The extent of precipitation increased with the concentration of piroxicam in the solution. Raman spectroscopy revealed that piroxicam precipitated as the monohydrate form.

\textbf{Conclusion}

An integrated analytical platform for detailed investigation of supersaturation, precipitation and dissolution events was developed. The open design of the flow-through cell allows detailed characterization using UV-Vis imaging, light microscopy and Raman spectroscopy. The setup may be of use for characterizing drug candidates intended for oral administration as well as for substances for injection where in situ forming drug delivery systems are explored. Further work will be focused on optimizing flow cell geometries and flow regimes.