Measurement of dissolution from a single crystal

UV imaging is a powerful tool to conduct advanced dissolution studies during drug development as it is capable of providing spatially and temporally resolved information. Detailed insights into the dissolution process such as face-specific/dependent dissolution can be attained from studies performed on single crystals. For example monitoring dissolution at the aqueous-solid interface of a crystal can provide information on the rate-limiting steps of the dissolution process \(^1\). In addition, measurements of concentration gradients in the vicinity of the solid surface may lead to knowledge of the relative importance of diffusion and convective currents to dissolution rates. Furthermore, dissolution studies conducted under conditions with little or no convective currents due to flow or agitation may also be of relevance, for example, crystal suspensions intended for parenteral administration such as subcutaneous, intra-muscular or intra-articular administration routes. Up until now such studies have been technically challenging. Here we show the use of the Sirius SDI (Figure 1) for the measurement of dissolution of lidocaine from a single crystal.

**Experimental**

UV imaging was performed using the Sirius SDI at 254 nm. A syringe pump was used for the infusion of the dissolution medium and the light source was a pulsed Xe lamp. The dissolution cell was filled with 0.067 M (pH 7.4) sodium phosphate buffer at room temperature, and dark (lamp turned off) as well as reference images were recorded. A single crystal of lidocaine 3 mm in length was placed within a hole in the base of the quartz dissolution cell (Figure 2), the flow was stopped to static conditions, and spatially and temporally resolved mapping of lidocaine concentration during the dissolution process was achieved from the recorded images. Calibration curves were constructed and the amount of lidocaine dissolved was determined by averaging absorbance values over the imaging area.

**Results**

Figure 3a shows the dissolution of lidocaine into the cell volume in the form of a UV absorbance map obtained at 254 nm (shown in enhanced colour). The vertically positioned lidocaine crystal almost reaches the top of the dissolution cell, and is apparent as an increase in absorbance. The dissolved lidocaine distributes primarily to the base of the cell as a result of the crystal dissolving within the additional space inside the hole not fully taken up by the inserted crystal.

Diffusion of dissolved lidocaine away from the crystal surface is expected to provide a symmetrical concentration distribution around the crystal in the stagnant liquid.
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Figure 3: Formation of concentration gradients.
Dissolution at pH 7.4 of a single crystal of Lidocaine. Isoabsorbance (isoconcentration) profiles are obtained by UV imaging 5 minutes after experimental onset.

3a (Left): The region of highest UV absorbance shown in red denotes the highest solution concentration; the region of lowest UV absorbance is shown in light blue.
3b (Right): Lines are isoabsorbance, where numbers represent concentrations in millimolar.

However, convection due to density gradients may, in addition to diffusion, affect the concentration distribution upon dissolution of lidocaine from the crystal. The importance of natural convection and density gradients on dissolution behaviour can therefore be spatially imaged in real time with this technology.

Figure 3b shows isoabsorbance contours for a selected image during single-crystal dissolution, readily converted into isoconcentration profiles using the molar absorptivity determined from the calibration curve.

Conclusion

UV imaging can be applied to monitor single-crystal dissolution of drug substances. The UV imaging detector facilitates monitoring of drug substance concentrations in dissolution media immediately adjacent to a single crystal of lidocaine in a spatially and temporally resolved format. This ability to attain two-dimensional images of the dissolution process provides a new insight into the dissolution process of single crystals, as it is difficult to study natural convection phenomena due to local density gradients using other current dissolution models. Under stagnant conditions, the importance of density gradients was revealed for lidocaine dissolution, where a concentration map showed the effects of natural convection on the dissolution process of lidocaine. Therefore UV imaging can provide a more detailed understanding for in vitro drug dissolution testing such as the measurement of dissolution from single crystals.

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References