Monitoring Lidocaine Single-Crystal Dissolution by Ultraviolet Imaging

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ABSTRACT: Dissolution critically affects the bioavailability of Biopharmaceutics Classification System class 2 compounds. When unexpected dissolution behaviour occurs, detailed studies using high information content technologies are warranted. In the present study, an evaluation of real-time ultraviolet (UV) imaging for conducting single-crystal dissolution studies was performed. Using lidocaine as a model compound, the aim was to develop a setup capable of monitoring and quantifying the dissolution of lidocaine into a phosphate buffer, pH 7.4, under stagnant conditions. A single crystal of lidocaine was placed in the quartz dissolution cell and UV imaging was performed at 254 nm. Spatially and temporally resolved mapping of lidocaine concentration during the dissolution process was achieved from the recorded images. UV imaging facilitated the monitoring of lidocaine concentrations in the dissolution media adjacent to the single crystals. The concentration maps revealed the effects of natural convection due to density gradients on the dissolution process of lidocaine. UV imaging has great potential for *in vitro* drug dissolution testing. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:3405–3410, 2011

Keywords: crystals; dissolution; dissolution rate; imaging methods; natural convection; UV/Vis spectroscopy; UV imaging

INTRODUCTION

Dissolution is frequently the limiting or rate-controlling step in drug absorption of poorly water-soluble drugs.[1–4] The commonly used *in vitro* dissolution methods including rotating disc, USP (United States Pharmacopeia) paddle and basket require relatively large amounts of drug substance and/or dissolution media. A current trend in drug development is to explore the physical properties of active compounds using high-throughput technologies and to use the identified solid forms (salt, polymorphic, solvate, co-crystal and amorphous) as a central part of product development.[5] Thus, micro-dissolution techniques requiring only a few milligrams of material, which may be of particular interest in early drug development, have been developed to overcome limitations related to dissolution testing.[6–8] In the above-mentioned methods, the concentration of dissolved substance is measured as a function of time in the bulk release media. Alternatively, for example, in the case of unexpected dissolution behaviour, more detailed information might be gained by monitoring the dissolution process immediately next to the surface of a small amount of the dissolving material. Imaging techniques capable of providing spectrally, spatially and temporally resolved information are emerging tools in more detailed studies of drug dissolution due to their potentially high information content.[9–15] Ultraviolet (UV) imaging technology, which has recently become commercially available, may constitute an alternative and complementary technology to, for instance, Fourier transform infrared and magnetic resonance imaging. UV imaging has the ability to generate visual images from simultaneous spectroscopic, spatial and time data. With UV imaging, it is possible to measure the intensity of light in the UV range passing through an area of a quartz tube as a function of position and time.[16] Thus, UV imaging may facilitate quantification of drug substances

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in solution immediately adjacent to the solid material and recording of concentration maps, spatially and temporarily resolved. Detection in the UV range is suitable for most drug substances; UV imaging will therefore be a widely applicable format for conducting advanced drug dissolution studies in drug development. For instance, monitoring dissolution at the aqueous–solid interface of a crystal may provide information on the rate-limiting steps of the dissolution process.[17] It has been shown that detailed insights into the dissolution processes, for example, face-specific/dependent dissolution,[18–21] may be attained from dissolution studies performed on single crystals. Such studies are, however, at present technically challenging. In addition, measurements of concentration gradients in the vicinity of the solid surface may lead to knowledge on the relative importance of diffusion and convective currents to dissolution rates. To this end, the influence of natural convection caused by density gradients on drug dissolution has been demonstrated.[22–24] 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, that is, subcutaneous, intra-muscular or intra-articular administration routes.

The objective of the present investigation was to perform an evaluation of the applicability of a commercially available UV imaging detector for conducting dissolution studies. Using lidocaine as a model compound, the aim was to develop a simple setup for measuring the dissolution of lidocaine from a single crystal into aqueous buffer. Dissolution of lidocaine into 0.067 M phosphate buffer (pH 7.40) was selected as an initial model system for UV imaging due to previous experiences related to intra-articular drug delivery,[25] the high aqueous solubility and associated rapid dissolution allowing short experimental times.

MATERIALS AND METHODS

Chemicals and Reagents

Lidocaine (Ph Eur (European Pharmacopoeia) 6th ed.) was obtained from Unikem, Copenhagen, Denmark. Lidocaine single crystals for the dissolution experiments were obtained from the recrystallisation of lidocaine in *n*-hexane.[26] Both the starting material and recrystallised lidocaine were identified to be monoclinic ($P2_1/c$) lidocaine, using X-ray powder diffractometry.[27] Sodium dihydrogenphosphate monohydrate was obtained from Merck (Darmstadt, Germany). The dissolution medium used was 0.067 M sodium phosphate, pH 7.40. Purified water from a Milli-Q deionisation unit (Millipore, Bedford, Massachusetts) was used throughout the study.

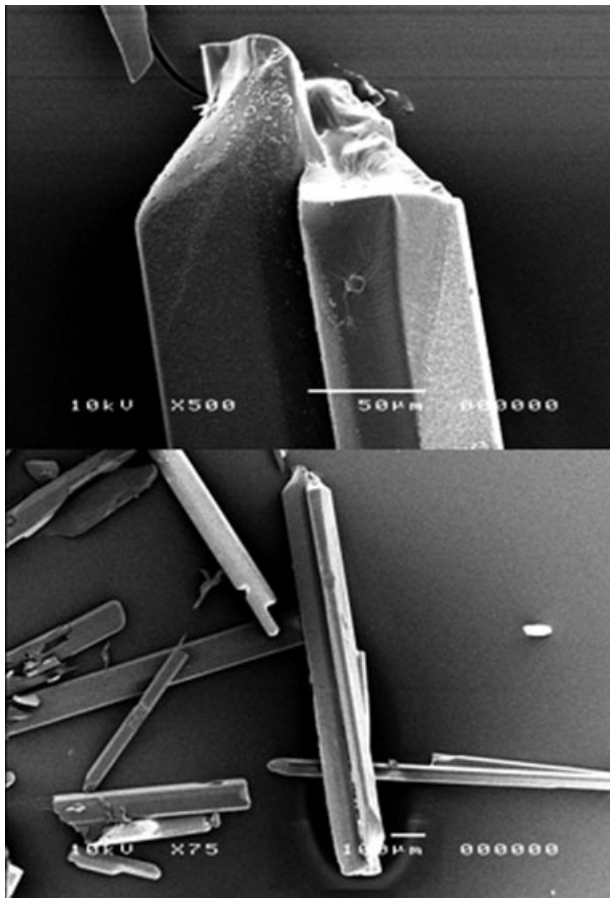

Figure 1. Scanning electron micrographs of lidocaine crystals.

UV Imaging Setup

UV imaging was performed using an Actipix SDI300 dissolution imaging system (Paraytec Ltd., York, United Kingdom) with Actipix flow-through type dissolution cartridges (supporting information Fig. 1). A syringe pump was used for the infusion of the dissolution medium and the lidocaine standard solutions. The total detection area of the UV imaging system is $9 \times 7\,mm^2$ (1280×1024 pixels); however, the selected imaging area was $9 \times 5.5\,mm^2$. The pixels ($7 \times 7\,\mu m^2$) were binned 4×4. The light source is a pulsed Xe lamp, and imaging was performed at 254 nm. The quartz dissolution cell [$7.5 \times 3.0 \times 63\,mm^3$ (height $\times$ width $\times$ length)] contained approximately 0.56 mL of dissolution media with the flow-through inserts in place. Images were recorded (2.3–2.6 images per second) and analysed using Actipix D100 software version 1.3 (Paraytec Ltd. York, United Kingdom). Pixel intensities were converted into absorbance using the Actipix software,[16] allowing the concentration of lidocaine within the imaging area as a function of position and time to be determined by the use of a calibration curve. The procedures for constructing calibration curves were similar to those reported previously.[16]

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