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Communication

Insights into amlodipine besilate dissolution behavior using UV imaging and Raman spectroscopy

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Abstract: In this work a UV imaging method was used to characterize the dissolution behavior of amlodipine besilate solid state forms. UV imaging encompasses the capability to obtain spatially and temporarily resolved absorbance maps of the solution phase. This technique provided visual indications that the amorphous form had a higher dissolution rate than that of the dihydrate form and that the amorphous form was subjected to crystallization. Furthermore, Raman spectroscopy showed that the thermodynamically metastable amorphous form converted to the monohydrate whereas the thermodynamically stable dihydrate form did not convert during dissolution testing.

Keywords: UV imaging; Dissolution; Solid state transformations; Raman spectroscopy; Amorphous; Crystalline

1. Introduction

UV imaging[1] enables the real time visualization of a solution concentrations at the immediate vicinity of a solid surface. This provides new possibilities in the investigation of the dissolution process and allows the capture of the initial stages of the dissolution process that most often are missed in traditional dissolution testing.

2. Experimental section

Monohydrate (MH) and dihydrate (DH) forms of amlodipine besilate (AMB) were prepared by recrystallization of AMB anhydrate in water. The amorphous form (AM) of AMB was prepared by dehydration of the MH form. The samples for UV imaging and Raman were compacted by weighing of 6 mg of substance into a steel cylinder (Ø: 2 mm) using a manual press (ActiPress, Paraytec Ltd., York, UK). A torque screwdriver was used to obtain the same compression force for all samples. Light microscopy and Raman spectroscopy were utilized before and after UV imaging for solid form identification.

Dissolution method

UV imaging was performed at 280 nm using an ActiPixTM SDI300 Surface Dissolution Imaging System (Paraytec Ltd, York, UK). The total imaging area was 9 mm x 7 mm (3 mm light path) and the dissolution cell had a volume of 560 µl (Figure 1). All experiments were carried out at ambient temperature (20 ˚C to 23 ˚C). The procedure for UV imaging was as follows: dark images (lamp turned off for 10 s) and reference images (10 s) were recorded with the dissolution cell filled with dissolution media (acetate buffer, pH 3.50 (Ph. Eur.)). After 60 s of data collection, the recording was paused, and the compact was inserted. After placing the compact containing either DH or AM, data collection was resumed, and the dissolution cell was filled with dissolution media (1 mL/min). This flow was arrested as soon as the dissolution cell was filled and the UV images were collected for 10 min in the absence of flow.

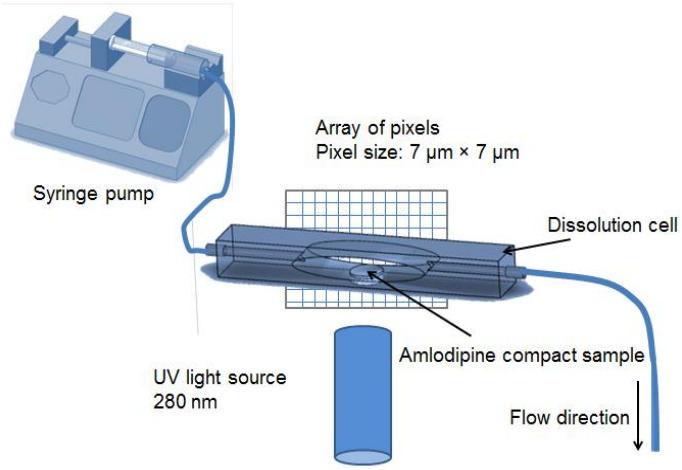

Figure 1 Schematic representation of the UV imager

3. Results and discussion

The UV imaging technique facilitated the acquisition of spatially and temporarily resolved intrinsic dissolution data of both AM and DH forms. Figure 2 show the absorbance maps at different time points where intense red color indicates high absorbance values and the contours depict lines with similar absorbance values. The outer blue contour line has a value of 400 mAU which is the equivalent of a 0.6 mg/mL solution concentration of amlodipine besilate. It is observed from the absorbance maps of the two forms that the AM sample has a faster dissolution than the DH sample. This faster dissolution of the AM sample is visualized directly by the greater area spanned by the AM sample contour lines. This was also expected since the AM sample is the metastable form of amlodipine besilate.

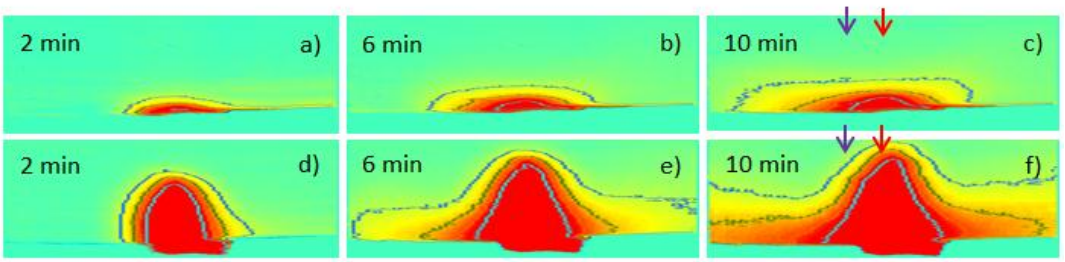

Figure 2 UV images of the two solid state forms at static conditions a-c: Amlodipine besilate dihydrate sample and d-f: Amorphous amlodipine besilate sample (the contour lines has the following absorbance values: blue 400 mAU, green 800 mAU, khaki 1200 mAU and cyan 1600 mAU)

Both the AM and DH samples are affected by a gravitational effect on the amlodipine besilate solution since both forms have a concentration accumulation in the lower part of the UV images which corresponds to the bottom part of the dissolution cell (Figure 2). Furthermore, it is observed that the contour profiles of the DH and AM samples are different from one another. The AM sample exhibit contour lines that are shifted upwards in the center of the UV images (red arrows) compared to off center (purple arrows). This shift is caused by a change in surface height, and thereby indicates crystallization of the AM sample, which was also apparent from the light microscopy photos (Figure 3) and visual inspection. The light microscopy photos show that the AM form change from a smooth glassy appearance to a more rugged shape that extends beyond the physical boundaries of the cylindrical compact whereas the DH form does not experience this change in the surface height during dissolution.

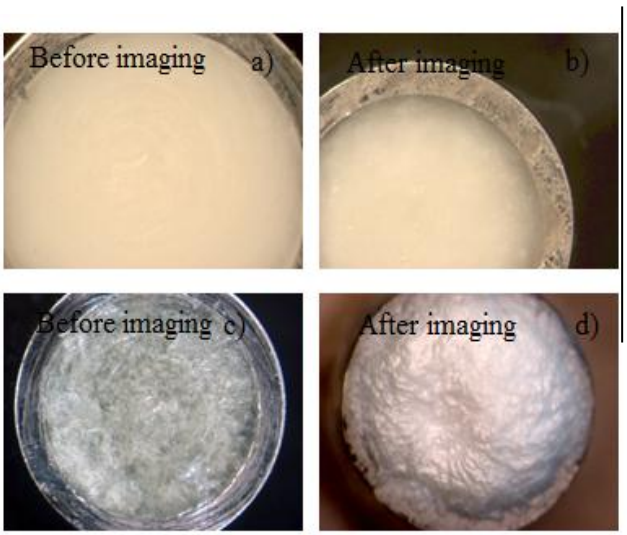

Figure 3 Light microscopy photos of the compacts containing the two solid state forms prior to and after UV imaging a-b: Amlodipine besilate dihydrate sample and c-d: Amorphous amlodipine besilate sample

In order to further investigate the complex behavior of the AM form, Raman spectroscopy was utilized (Figure 4a). The Raman data showed that the DH samples did not convert during dissolution. However, Raman spectroscopy showed that the thermodynamically metastable AM sample converted into the monohydrate upon contact with the dissolution media.

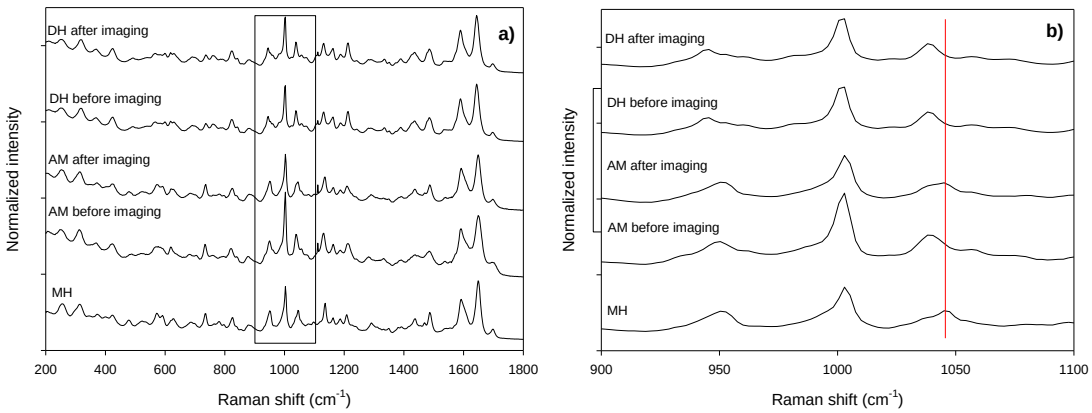

Figure 4 Raman spectra of the compact of dihydrate and amorphous solid forms prior to and after dissolution testing. The monohydrate form has been inserted for comparison (a) the whole Raman spectra (b) Magnification of the region from 900 cm^{-1} to 1100 cm^{-1}

The conversion of the AM form to the MH form was apparent as a peak shift from 1038 cm^{-1} to 1045 cm^{-1} (marked with red line in Figure 4b). No further conversion of the monohydrate to the dihydrate form was observed, which is in accordance with previous findings since the kinetics of this transformation has been reported to be relatively slow (occurring after 19 h of contact with aqueous medium at 37 ˚C).[2] This conversion of the AM to the MH form and the concomitant non-controllable change in surface area of the sample present several analytical challenges in relation to the assessment

of the dissolution of the AM form. First of all, the absorbance values observed in the UV images (Figure 2) can either be due to the solution concentration, solid form precipitation blocking the light path or a combination of both. Experiments conducted using a higher wavelength where the dissolved amlodipine besilate does not absorb light may in future be helpful in discriminating between solid material and material in solution. Secondly, the generated MH form has a slower dissolution than the starting AM form.[2] This formation of the more stable MH form also constitutes a challenge that would have to be elucidated in future studies by using e.g. in-situ Raman spectroscopy[3] and thereby obtaining solid phase information during dissolution. Finally, it is difficult from these static measurements to assess the quantitative dissolution rates of the samples. A possible way to obtain such information is by utilizing flow experiments, where the dissolution rates can be calculated from the flux of material into solution.

4. Conclusion

The spatially and temporarily resolved absorbance data enabled by UV imaging revealed a difference between the dissolution of AM and DH samples. The AM samples crystallized during the dissolution experiment, which was verified by Raman spectroscopy. The AM sample experienced an increase in surface area generated by the crystallization the MH form, this increase in surface area was directly observable with the UV imaging technique. This was not the case for the DH sample since no crystallization occurred for this compound. Further development of the UV imaging technique within this area is in progress in order to elucidate these complex solid form transformations.

References and notes

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