Pharmaceutical Compounds Studied Using NEXAFS

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Abstract. Total Electron Yield (TEY) oxygen K-edge NEXAFS detects the presence of strongly adsorbed water molecules on poloxamer-coated pharmaceutical actives, which provides a useful spectroscopic indicator for bioavailability. The results are supported by complementary XPS measurements. Carbon K-edge spectra obtained in a high-pressure NEXAFS cell were used *in situ* to establish how a polymer coating spread on a drug surface by using humidity induced dispersion of the coating. Finally, we demonstrate how combined Carbon and Oxygen K-edge measurements can be used to characterize amorphous surface layers on micronised crystals of a drug compound.

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INTRODUCTION

The pharmaceutical industry spends upwards of £3 billion in the U.K. alone on developing new drug actives each year [1]. Favorable physiological and biochemical properties of new compounds are often accompanied by undesirable physical properties (solubility, polymorphism, surface structures) that make them unsuitable for formulation into a format in which they can be reliably delivered to the human body. Control, modification, characterization and functionalisation of surface properties at the molecular level is then often essential to enable the preparation of stable suspensions or soluble with surfactants. Commonly used analytical techniques in the pharmaceutical industry include X-ray powder diffraction, FTIR/Raman spectroscopy and solid state NMR, but these techniques lack the surface sensitivity required to study interactions at the molecular level. In contrast, commonly used surface-sensitive techniques such as Dynamic Vapour Sorption (DVS) and Atomic Force Microscopy (AFM) provide only limited information on chemical composition. We have now employed a combination of NEXAFS and XPS to study pharmaceutical actives with a view to addressing a number of specific problems.

POLYMER COATINGS

Poor water solubility is a major problem for many new drug products with up to 80% of new drug molecules being insoluble in water [2], thus leading to poor bioavailability. The use of polymer surfactants to improve uptake in poorly soluble compounds is well established [3] and XAS can provide important new insights into their application. Two polymer coated drug compounds were studied, A and B.

Drug A

Six samples of the drug were prepared with increasing levels of a polypropylene-polyethylene co-polymer (poloxamer) to improve bioavailability. It was found through solubility studies that increasing coating levels did not monotonously scale with increases in bioavailability. NEXAFS was used to investigate this behaviour.

C, N and O K-edge spectra were measured on the 5U.1 undulator beamline of the SRS using a combined Total Electron Yield (TEY) / Fluorescence Yield (FY) cell. The FY spectra shown in Figure 1 are characterized by a strong π^*-resonance, A, and two σ^* resonances, B and C. These stem from, respectively, double- and single-bonded O-containing functional groups in the drug compound. There are no significant differences between these FY spectra, indicating that no bulk changes were introduced by the coating process.

Figure 2 shows the corresponding O K TEY spectra. They are again characterized by the strong π^* resonance, A, and the σ^* resonance, B, while resonance C appears almost entirely masked by

additional spectral contributions from the adsorbate layer. In some spectra weak additional peaks are visible between A and B. These additional peaks are the signature of adsorbed water [4], and they are particularly prominent in the third spectrum from the top. Interestingly, the corresponding sample also showed the highest uptake rates in drug trials. It appears that the ability of this sample to bind more water and/or to bind it more strongly may be associated with higher solubilisation rates, and thus improved delivery to the human body. It should also be noted that the pure drug (top spectrum) exhibited similar evidence for strongly adsorbed water, suggesting that a cooperative effect involving both the ability to bind water *and* the presence of a poloxamer layer is necessary to improve bioavailability.

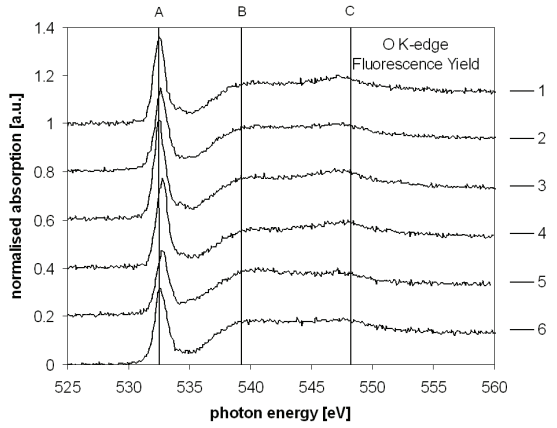

FIGURE 1. O K-Edge FY NEXAFS spectra of coated drug A samples, which were prepared by adsorption of poloxamer from 6 different solutions with increasing concentrations (sample 1 represents the pure drug, sample 6 the highest poloxamer concentration in solution).

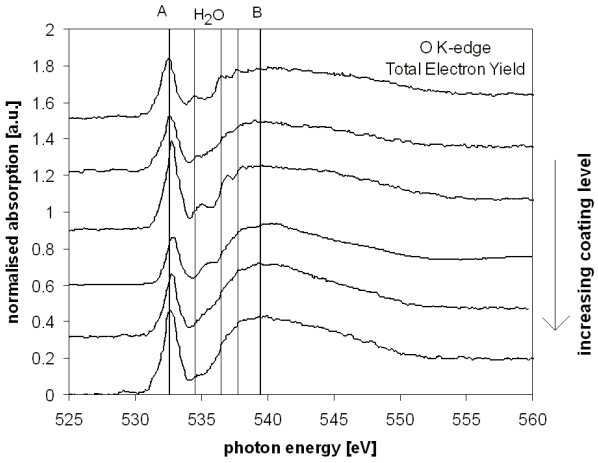

FIGURE 2. O K-Edge TEY NEXAFS Spectra of drug A. The order of the spectra from top to bottom is as described in the caption of fig. 1.

Drug B

Samples of a different drug, B, were coated with a series of commonly used polymers such as poloxamer, polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) to achieve enhanced solubilisation. C K-edge TEY spectra were measured on the 6.1 multipole wiggler beamline of the SRS and O K edge spectra were measured on the 5.1 undulator beamline. Relative humidity (%RH) control was achieved by dosing water vapour onto a nitrogen gas cooled sample plate.

Figure 3 shows that the pure drug has a distinct pre-edge feature in the C K-edge spectrum. It remains present in the PEG-coated spectra, suggesting that either the polymer is present as a very thin (mono)layer, which does not attenuate the substrate signal very much, or it is present in multilayer patches which do not completely cover the drug surface.

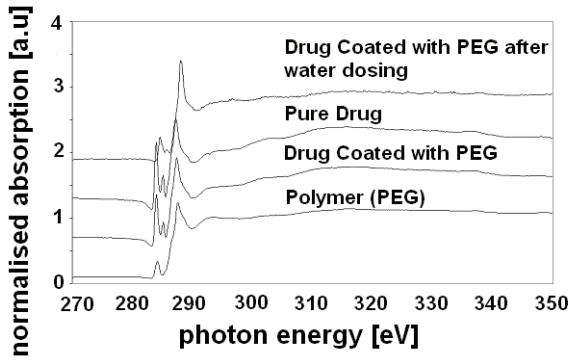

FIGURE 3. C K-Edge NEXAFS of Drug B.

That the latter is the case is strongly supported by the fact that exposure to 100% RH suppresses the signal from the drug substrate entirely and irreversibly (removal of water vapour does not lead to the reappearance of the drug substrate spectrum). It appears that the PEG multilayer patches are enabled to wet the drug surface when given enough mobility through the high relative humidity. Further support for this interpretation of the spectral changes comes from the fact that the suppression of the drug substrate signal was observed both in NEXAFS and XPS. We note that because of their different surface sensitivities [5,6] the combination of both techniques can at least semi-quantitatively determine the coverage of the particular polymer and hence how effective it is at coating the drug.

AMORPHOUS SURFACES

An amorphous drug formulation will generally have higher dissolution rates than a crystalline one [7].

However, the amorphous state is also more susceptible to environmental changes such as temperature and humidity, making it important to have the amorphous and crystalline content of a drug substance well characterized [8]. Surface effects easily escape analysis with commonly used laboratory techniques (*vide supra*) but will have a disproportionately greater effect on uptake in the body.

Drug C

Crystalline and X-ray diffraction-amorphous samples of drug C were investigated. In addition, batches of the crystalline sample were milled to μm-sized particles (micronised) for product formulation purposes. Figure 4 shows that NEXAFS at the C K-edge distinguishes between the amorphous and crystalline reference compounds, most clearly visible through the presence of an increased π* resonance in the amorphous form. The C K edge of the micronised compound almost entirely resembles the spectrum of the amorphous form, suggesting that the milling process resulted in a surface layer that was essentially amorphous.

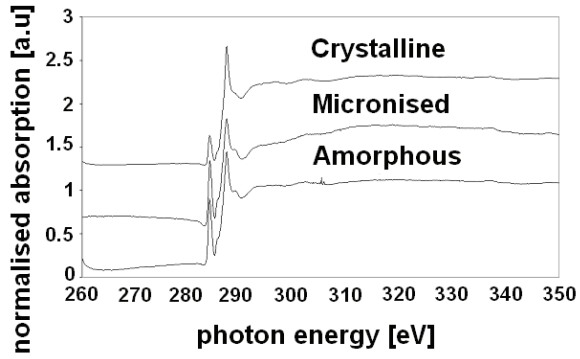

FIGURE 4. Carbon K-Edge NEXAFS Spectra of Drug C

At the O K-edge the crystalline sample has a sharper π* resonance than the amorphous sample which has a shoulder on the high energy side (data not shown). The Micronised sample shows an intermediate spectra, which was fitted to obtain a composition of approximately 75% crystalline 25% amorphous. This can be explained by the surface amorphous layer being only a few nm thick, with the differences in amorphous content being explained by differences in the sampling depth between the C and O K-edges.

CONCLUSIONS

We have demonstrated that C and O K-edge NEXAFS provides useful information on the surface properties of complex organic molecular materials such as pharmaceutical drugs. The presence of strongly adsorbed water on a poloxamer-coated pharmaceutical appears to be a good indicator for improvements in bioavailability. Information on the morphology of polymer coatings and of dynamic changes due to humidity changes was obtained. The use of the amorphous state in pharmaceuticals is of increasing importance and we found that NEXAFS is suited to study the influences of environmental conditions on the difficult to characterize thin amorphous surface layers. The ability to rapidly examine the surface properties of drug compounds and their formulations by NEXAFS in an environmental chamber with quick sample turnover could be used for rapid screening, resulting potentially in significant cost savings in drug development.

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