NEXAFS Studies of Pharmaceutical Formulations

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Introduction

The pharmaceutical industry spends upwards of £3 billion in the U.K. alone on developing new drugs each year [1]. Favourable physiological and biochemical properties of new compounds are often accompanied by undesirable physical properties (solubility, polymorphism, surface structures) that make them unsuitable for formulations that can be reliably delivered to the human body [2,3]. For example, the control, modification, and characterisation of surfaces properties at the molecular level is often essential to develop methods for surface functionalisation that enable the preparation of stable suspensions or of solubilisation.

The most commonly used analytical techniques in the pharmaceutical industry include bulk probes such as X-ray powder diffraction, FTIR/Raman spectroscopy and solid state NMR [4]. Often used surface-sensitive techniques are Dynamic Vapour Sorption (DVS) and Atomic Force Microscopy (AFM), but these provide only limited information on chemical composition. We have now employed a combination of Near Edge X-ray Absoption Fine Structure (NEXAFS) and X-ray Photoelectron Spectroscopy (XPS) to overcome these limitations in pharmaceutical research and with a view to addressing a number of specific problems.

Results and Discussions

Here we present re[resentative results for two different drug compounds, which were studied as test systems for the applicability of NEXAFS and XPS. Fig. 1 shows O K-edge NEXAFS data for several formulations of compound 1, which were prepared with increasing amounts of a polymer coating to improve bioavailability. It was found in practice that increasing coating levels did not always lead to better bioavailability of the drug. The NEXAFS data in Fig. 1 provide a possible explanation for this behaviour. The spectra are dominated by a π^* resonance, A, and a σ^* resonance, B. In some spectra weak additional peaks are visible between A and B. These additional peaks are associated with adsorbed water, and they are particularly prominent in the third spectrum from the top. Interestingly, the correwsponding sample also showed the highest metabolic uptake rates in drug trials. It appears that the ability of this sample to bind more water and/or to bind it more strongly is associated with better solubilisation, and thus improved delivery to the human body.

In a second study, formulations of another poorly water-soluble compound were prepared with several different polymer surfactants to achieve enhanced solubilisation. Fig. 2 shows XP spectra of the untreated sample and a sample coated in PEG (polyethylene glycol). With the coated sample there are two additional peaks in the XPS data. The emission at approximately 529 eV stems from the coating, while the strong emission at approximately 531 eV is due to adsorbed water. Again, the presence of adsorbed water was found to be closely associated with the efficiency of the coating in improving uptake by the human body. Note also that there is still a signal

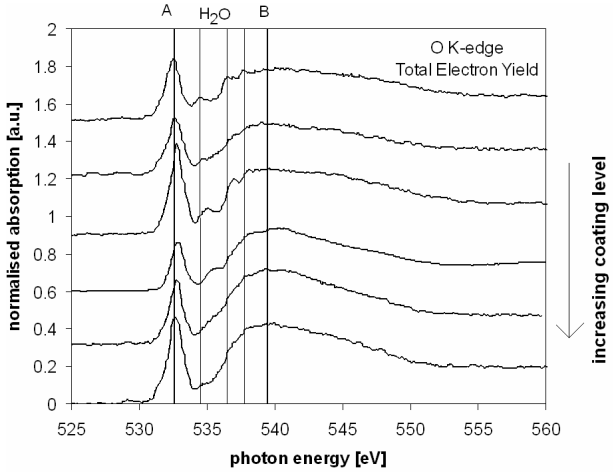

Fig. 1. NEXAFS spectra showing of a drug with an increasingly thick polymer coating.

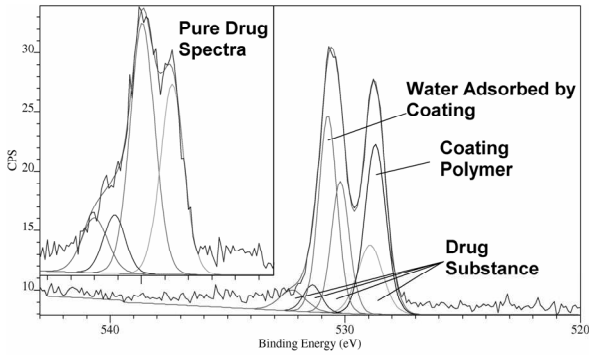

Fig. 2. XP spectra of a pharmaceutical formulation illustrating the surface coponents.

from the drug substrate, which suggests that the coating is present either as a very thin layer or in patches that leave part of the drug surface exposed.

Conclusions

The presence of adsorbed water on coated pharmaceuticals appears to be a good indicator of improvement in bioavailability. Formulation screens by X-ray spectroscopy may facilitate more focussed clinical trials, resulting potentially in significant cost savings.

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