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Multivariate calibration of energy-dispersive X-ray diffraction data for predicting the composition of pharmaceutical tablets in packaging

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ABSTRACT

A system using energy-dispersive X-ray diffraction (EDXRD) has been developed and tested using multivariate calibration for the quantitative analysis of tablet-form mixtures of common pharmaceutical ingredients. A principal advantage of EDXRD over the more traditional and common angular dispersive X-ray diffraction technique (ADXRD) is the potential of EDXRD to analyse tablets within their packaging, due to the higher energy X-rays used.

In the experiment, a series of caffeine, paracetamol and microcrystalline cellulose mixtures were prepared and pressed into tablets. EDXRD profiles were recorded on each sample and a principal component analysis (PCA) was carried out in both unpackaged and packaged scenarios. In both cases the first two principal components explained >98% of the between-sample variance. The PCA projected the sample profiles into two dimensional principal component space in close accordance to their ternary mixture design, demonstrating the discriminating potential of the EDXRD system.

A partial least squares regression (PLSR) model was built with the samples and was validated using leave-one-out cross-validation. Low prediction errors of between 2% and 4% for both unpackaged and packaged tablets were obtained for all three chemical compounds. The prediction capability through packaging demonstrates a truly non-destructive method for quantifying tablet composition and demonstrates good potential for EDXRD to be applied in the field of counterfeit medicine screening and pharmaceutical quality control.

1. Introduction

EDXRD is a powerful tool for characterizing the chemical composition of crystalline materials. Materials which fall into this category include powder-form illicit drugs and plastic explosives, both of which have been studied using EDXRD [1–3]. The advantages of this technique include the use of high-energy photons which are capable of penetrating the surface of materials and characterising the layers beneath. This is a highly attractive capability in security screening contexts and for the determination of medicine quality. In both types of context a low level of disruption is desirable and EDXRD provides a non-destructive and non-invasive means of testing. A recent study has demonstrated that chemically-relevant features from EDXRD data can be observed for aspirin tablets when they are within blister packaging [4]. A quantitative analysis of unpackaged pharmaceutical formulations using EDXRD and multivariate calibration methods was carried out in a previous study and demonstrated good capability to predict concentrations of the constituent compounds [5]. In the present study we demonstrate again this capability and extend it to modelling and quantifying the chemical composition of the same samples through blister and card packaging simultaneously.

There are many examples of Raman spectroscopy being combined with multivariate calibration for quantitative analysis of pharmaceutical mixtures [6–10]. One such study [10] looked at ternary mixtures of paracetamol, starch and sucrose, covering a range of concentrations. The Raman spectra were acquired through blister packaging to construct a partial least squares (PLS) regression model, resulting in a root mean square error of cross validation (RMSECV) of 1.4%, and the authors observed the potential application to counterfeit medicines detection. Fraser et al. carried out a semi-quantitative analysis of active pharmaceutical ingredients (APIs) in intact tablets of erectile dysfunction medicines, including counterfeit versions – the PLS calibration model in this case was constructed from Raman spectra from tablet 'cores', i.e. with

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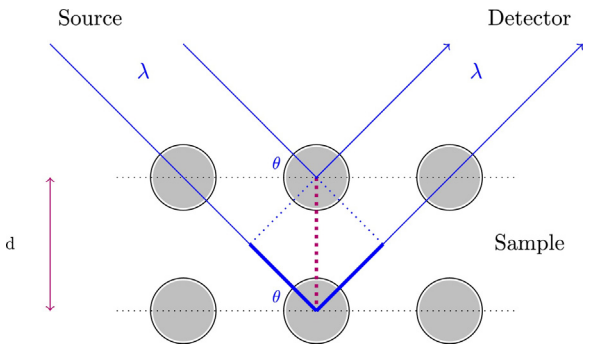

Fig. 1. X-ray incident on two parallel planes at an angle θ, with photon wavelength λ and planar spacing d. The thicker ray line represents the additional path length traversed in a reflection from the lower plane which, for a coherent scattering event, is an integer multiple of the X-ray wavelength, satisfying Bragg's law.

the coating removed. Using selected bands of the spectra and pre-processing, a RMSECV of 7.38% was achieved in the best case [9].

Several studies have combined ADXRD with PLSR on pharmaceutical mixtures often with comparisons made to Raman spectroscopy [11–17]. However, none of these studies analysed formulations within any form of packaging materials.

To the authors' knowledge, there have been no previous studies into the non-destructive quantitative analysis of pharmaceutical mixtures through packaging using EDXRD and chemometrics, which form the basis of this study. The following section introduces some principles of X-ray diffraction (XRD) to explain the physical phenomena giving rise to the features observed in the experimental data.

1.1. X-ray diffraction

Crystalline materials – such as polycrystalline powders of the chemicals used in pharmaceutical formulations – comprise molecules which are arranged in an ordered three-dimensional structure repeated throughout the crystal. Sets of parallel molecular planes arise from this long range order [18]. These sets of planes, in particular the separation between them, are unique to the material and thus present an opportunity for material identification. It is through XRD that we can achieve this characterisation of materials.

X-rays of the same energy scatter coherently from molecules in adjacent planes when constructive interference occurs. The conditions to be satisfied for the detection of a coherent scattering event are shown in Fig. 1 and are defined by Bragg's law:

$$n\lambda = 2d\sin\theta, \tag{1}$$

where λ is the wavelength of the incident X-ray, d is the interplanar spacing and θ is the angle subtended by the X-ray source, the sample and the detector.

There are two ways in which Bragg's Law can be interpreted for use in XRD experiments. Firstly, in ADXRD, monochromatic X-rays are used (i.e. fixed λ) and diffraction peaks are detected for a range of angles. ADXRD provides high-resolution XRD profiles, but the relatively low energy X-rays used do not pass through thick samples. Secondly, in energy-dispersive XRD (EDXRD), the sample is irradiated with polychromatic X-rays and an energy-resolving detector collects a diffraction spectrum at a fixed angle. The quality of diffraction patterns is limited by the energy resolution of the detector, and more importantly, by the loss of angular resolution due to collimators allowing a range of angles, i.e. deviations from the nominal angle, of X-rays through. This is a necessary compromise in order to collect an adequate number of counts in an acceptable time scale for screening applications, but results in significantly broader, overlapping peaks compared to ADXRD profiles.

It is common to convert the energies of an EDXRD spectrum to units of momentum transfer x, which incorporates diffraction dependence on scattering angles and X-ray energy. This is useful for making comparisons between EDXRD systems, and between ADXRD and EDXRD. Bragg's law (1) is rearranged to:

$$x = \frac{1}{2d} = \frac{1}{\lambda}\sin\theta = \frac{E}{hc}\sin\theta, \tag{2}$$

using the relationship between energy of a photon and its wavelength:

$$\lambda = \frac{hc}{E}, \tag{3}$$

where h is Planck's constant c is the speed of light in vacuo.

The advantages of EDXRD are that the lack of moving parts in the instrumentation can make data collection more rapid and the higher energies of X-rays used can penetrate bulkier samples. EDXRD can therefore be used for non-destructive analysis of materials.

It is assumed that statistically, all possible orientations – and hence planes – of the crystals are represented equally in a powder. However, some crystals have shapes that create a tendency for them to align in a certain way, in which case some crystal planes are over-represented in the resulting diffraction pattern – this is the preferred orientation effect. This effect is often stated as being a limiting factor of the use of ADXRD in the aforementioned studies.

Another relevant physical phenomenon in X-ray screening is that of attenuation. Materials attenuate the beam and reduce the flux of photons which are transmitted through the material. Attenuation is greater for lower-energy photons as well as for thicker materials. Moreover, the molecular composition of the material itself has its own energy dependent attenuation profile, $\mu(E)$. The percentage of X-ray photons at an energy E which will be transmitted through a material of thickness x which has an attenuation coefficient of $\mu(E)$ is defined by the Beer–Lambert law:

$$I(E) = \exp(-\mu(E)x), \tag{4}$$

where I is the relative intensity of the X-ray beam at energy E following the interaction with the material. The effect of attenuation by packaged tablets at lower energies is therefore appreciable.

2. Materials and methods

2.1. Sample preparation

Paracetamol (Acetaminophen BioXtra, ≥99.0%; Sigma Aldrich), caffeine (ReagentPlus; Sigma Aldrich), and microcrystalline cellulose (average particle size 50 μm; Acros Organics) were the ingredients of the ternary mixtures and were all used as received. The former two are common APIs, and the latter is a common excipient used as a dilutant. Microcrystalline cellulose was an appropriate excipient as it has an XRD spectrum that is representative of other common excipients in terms of its peak broadness and momentum transfer range in its XRD profile.

The calibration mixture design is shown by the triangles in Fig. 2. Such a design simplex is common to mixture analysis experiments and has been used to enable the system to be compared to other studies [11,13].

Each sample mixture was ground with an agate mortar and pestle for three minutes to mix thoroughly and to reduce particle sizes – with the aim to decrease preferred orientation effects [13]. More vigorous mixing techniques such as milling were avoided to prevent potential polymorph phase transitions [11,13,15,19]. Sieving was also avoided as the paracetamol powder exhibited a build-up of electrostatic charge when ground, making it difficult to handle;