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Analysis of challenging pharmaceutical samples using chemical and elemental images

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Chemical images obtained using vibrational spectroscopic techniques (Raman, mid-IR and near-IR) have emerged as rapid, non-invasive means to assess the quality of a pharmaceutical formulation. A hyperspectral datacube, containing several thousand spatially resolved spectra, is acquired by combining vibrational spectroscopy with digital imaging or by rastering point measurements across a sample. This enables the spatial distribution and interaction of chemical components within the sampled area to be determined. This paper will discuss the use of vibrational spectroscopic methods in the analysis of challenging pharmaceutical samples.

Many formulations are now developed to control the release of the active pharmaceutical ingredient (API). The delivery of the API may be controlled in such a way as to allow the patient to receive the benefits of the API over an extended time period. Beads are often used for this purpose with an API layer, applied to a sugar core, being coated in a polymer layer that controls dissolution rates. Raman mapping has been successfully employed to better understand the workings of some bead formulations that are undergoing development. Drug migration into the control release layer has been identified to be the cause of a variation of the dissolution profile amongst some beads. Formulations developed to prevent this migration were shown to be successful, whilst ensuring product performance and stability.

Several other API delivery systems exist other than the oral route including dermal and transdermal delivery systems. Transdermal drug delivery is very successful in many cases such as nicotine or hormone replacement therapies. A good understanding of drug penetration through or into the skin barrier requires knowledge of the various layers that make up skin i.e. stratum corneum, epidermis and dermis. Vibrational spectroscopy has been widely used to analyse skin layers and skin conditions identifying spectroscopic characteristics for each [1,2,3]. By spectroscopic mapping it is possible to build up an image of the layers in a cross-section. Raman, mid-IR and near-IR mapping were all investigated as tools for producing chemical images of skin and have been compared with respect to their practical application. All of the techniques proved successful although sample preparation is key and slightly different approaches are required for each technique. Mid and near-IR methods are more practical in terms of speed taking minutes to hours to collect a map where a similar area by Raman mapping takes days.

In some circumstances components at very low concentrations within a pharmaceutical formulation, such as lubricants, may be difficult to identify using vibrational spectroscopic techniques. Scanning electron microscopy – energy dispersive X-Ray spectroscopy (SEM-EDS) offers an alternative for identifying some lubricants such as magnesium stearate. By using a low vacuum system, the sample requires no metal coating so the method is non-destructive and the sample can be analysed by vibrational methods post-SEM analysis. Initial studies on placebo formulations containing varying

proportions of Avicel™ (microcrystalline cellulose), dibasic calcium phosphate (DCP), lactose, Explotab™ (sodium starch glycolate) and 1% magnesium stearate have been used to compare results from Raman and SEM/EDS maps. Principal component analysis is required to analyse the Raman maps as most spectra have contributions from more than one component. This results from the close proximity and sometimes coating of one component with another. Figure 1 shows the principal component scores images that identify the four components present in the placebo. The SEM micrograph with overlaid EDS map of magnesium for this placebo is shown in Figure 2. A concentration of magnesium (as magnesium stearate) is found on a granule of DCP. DCP is a hard component and magnesium stearate softer so it may coat the harder material. The Raman and SEM-EDS data can be used to understand the make-up of the placebos and relate this to their physical properties and how they process during manufacture[4].

[1] P.J.Caspers et al., J Invest. Dermatol. 116 (2001) 434.
[2] B.W.Barry et al, J Raman Spectrosc. 23 (1992) 641.
[3] L.M.McIntosh et al, Vibrational Spectroscopy 28 (2002) 53.
[4] The collection of the SEM-EDS data by Gary Nichols of Pfizer Global R&D is gratefully acknowledged. The assistance of Fiona Clarke of Pfizer Global Manufacturing and Gavin Aston and Peter Batey of Perkin Elmer is acknowledged for the collection of mid and near-IR maps.

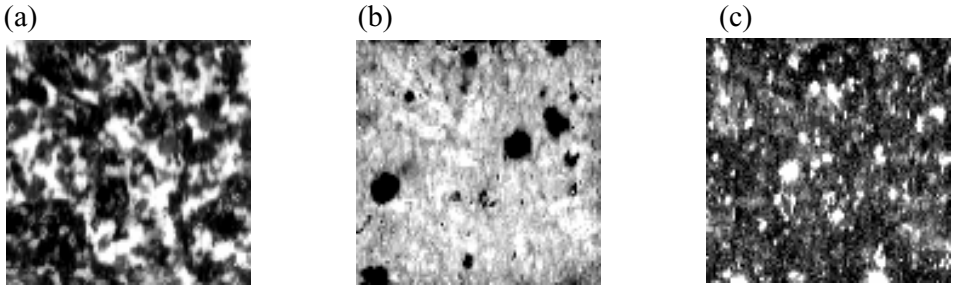

Fig. 1. Principal component scores images of a placebo formulation (500 x 500 μm) (a) Avicel (black particles) and DCP (white particles), (b) Explotab (black particles), and (c) magnesium stearate (white particles).

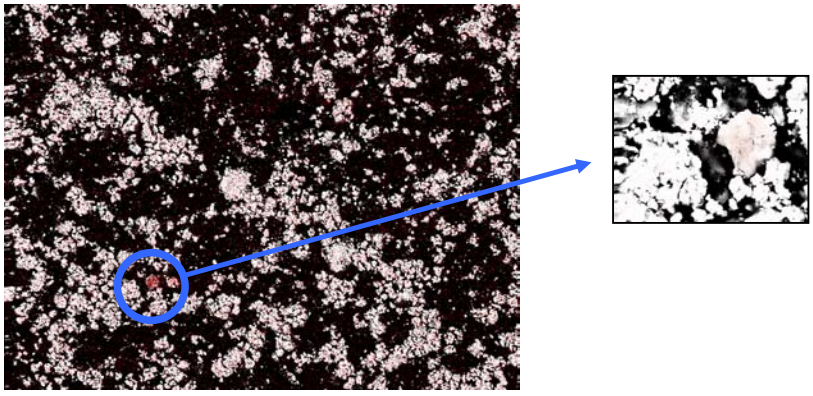

Fig. 2. Scanning electron micrograph of the placebo formulation showing DCP in a microcrystalline cellulose matrix. Overlaid is the EDS map for magnesium showing a concentrated amount of magnesium stearate on a granule of DCP.

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