

A near infrared view of pharmaceutical formulation analysis

E. Neil Lewis,^a John E. Carroll^b and Fiona Clarke^c (^aSpectral Dimensions Inc., Olney, MD, USA; ^bCadrai, Bel Air, MD, USA; ^cPfizer Central Research, Sandwich, Kent, UK; address correspondence to info@spectraldimensions.com)

Introduction

Pharmaceutical dosage forms consist of a mixture of ingredients combined to provide desirable characteristics. Called the *pharmaceutical formulation*, the dosage form is most often a tablet or capsule. The scale-up process that yields the most desirable dosage form is called formulation development. It is critical that the formulation be robust and consistent, any tablet or capsule produced anywhere in the world must have the same therapeutic characteristics. A basic problem in pharmaceutical manufacturing is that seemingly simple formulations with identical ingredients can exhibit radically different performance depending upon how the ingredients are blended together. The problem is compounded with newly-developed advanced drugs that contain small amounts of highly-potent active ingredients, administered via complex delivery systems.

Steve Hammond, manager of the Process Analytical Support Group for Pfizer Global Manufacturing, is responsible for maintaining the integrity of pharmaceutical production worldwide. He has published several articles^{1,2} describing the necessity of understanding the spatial relationship and interaction of drug formulations, and the current lack of analytical instrumentation to provide these data.

...the most significant factor in determining the quality of a formulated product, is the structure of the matrix that evolves during this manufacturing process... when it is time to assess the quality of our products, we invariably destroy the matrix by dissolving the sample in a solvent. All the information on the physical state of the ingredients and how they relate to each other is then effectively lost... Our plan is to establish the characteristics of a good matrix and a bad matrix, then to assess every new lot manufactured for its matrix conformity against the reference. [Steve Hammond, Pfizer Global Manufacturing, *European Pharma. Rev.* 3, 47 (1998)].

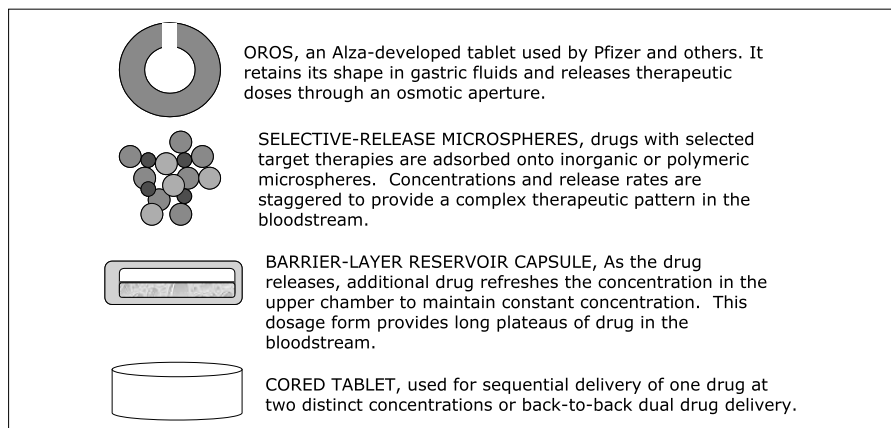


Figure 1. Examples of complex solid dosage forms.

As active ingredients become more powerful, drugs can deliver therapeutic performance with far lower concentrations than was possible even two years ago. An Aspirin[®] tablet contains 325 mg of the active principle, acetylsalicylic acid, whereas Viagra contains sildenafil citrate at therapeutic levels as low as 10 mg. Some heart medications are produced in 0.5 mg strengths. Even though the amount of active is decreased in these formulations, the tablet size cannot be reduced beyond the ability of the patient to handle it. Often, the proportion of inert excipients to the “active” is simply made higher so that the tablet remains about the same size as an Aspirin dosage unit. It is typical upon micro-examination of tablets to find active ingredients not evenly dispersed, but rather distributed in discrete particles or clumps. As dosage concentration drops, it is increasingly difficult to ensure content uniformity.

Pharmaceutical makers are also increasing drug dosage management—mixing drugs in a single dose, extending drug release from a single dosage form or providing longer, flatter bloodstream concentration profiles. HIV “cocktail” drugs are a good example. Lower active concentrations and more complex excipients often mean that conventional testing—dissolution, content uniformity and label-strength assay—become difficult to accomplish. More sophisticated analytical techniques are now needed in the formulation development phase

and throughout the production process to monitor these characteristics.

These new drug release systems are quite complex, requiring complicated tablet architecture as well as patient-friendly administration. This has given rise to a whole new engineering genre. Examples of some of the new solid dosage delivery forms—OROS tablets, mixed micro-spheres, barrier-layer capsules and cored tablets—are shown in Figure 1. Other advanced delivery systems used by the pharmaceutical industry includes inhalable aerosols, barrier-layer transdermal patches and “piggyback” lipid delivery systems. The regulatory testing stakes for each new delivery mechanism are high because they depend upon physical chemistry to deliver the drug. There are stringent regulatory requirements that must be met in order to market the drug.

Pharmaceutical companies are realising that existing analytical techniques are inadequate to characterise the properties that determine the potency of new, spatially-complex finished products. Existing workhorse analytical techniques such as HPLC and mass spectrometry are widely used to measure the gross composition of the finished product, yet shed no light on the distribution of the components. Dissolution studies can determine the manner and duration of component release but they are destructive, lengthy procedures and cannot provide insight into the cause of manufacturing defects. Increasing com-

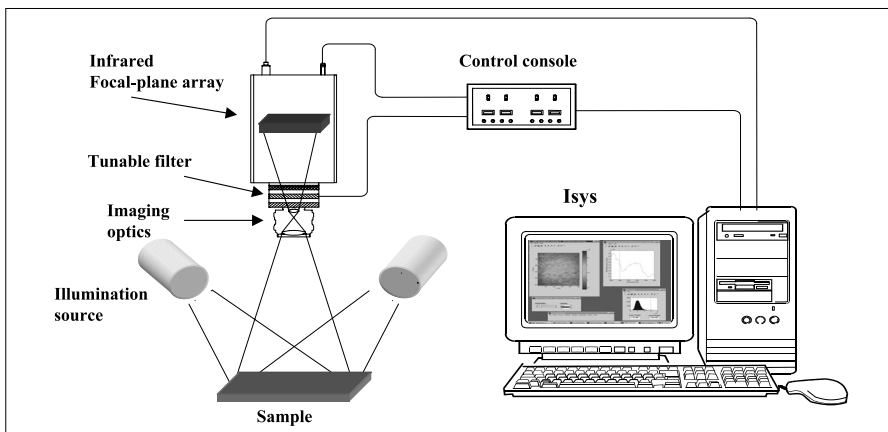


Figure 2. Simplified block diagram of Matrix NIR™ NIR spectral imaging system.

plexity in dosage delivery design and more potent active ingredients demand a method for rapid and direct visualisation of the spatial distribution of the chemical components that make up these products.

The problem is critical. Drug efficacy is dependent upon “blind” manufacturing processes that produce dosage forms that can only be tested after the fact. When defects occur, there is no fast, reliable analytical technique capable of pinpointing the source of the problem. Even when the process is in control, existing procedures are lengthy and may cause expensive production delays. Characterisation techniques that provide chemical and physical data that meet the criteria described by Hammond above are a necessity: complex drugs require more exacting testing techniques and faster information return rates than possible with existing analytical instrumentation. A related issue is the expense of product tied up in WIP (work in process) while testing is conducted. For a large company this can represent \$1 billion worth of inventory at any given time. A technique that improves testing turnaround can save millions of dollars, by decreasing time-to-market.

Non-imaging NIR spectroscopy is quickly becoming a workhorse analytical technique³ within the pharmaceutical industry for both qualitative and quantitative applications.^{4,5} It is widely used for the characterisation of raw materials^{6,7} and is becoming accepted for the analysis of intact tablets,^{8,9} blend homogeneity,^{10,11} particle size determination^{12,13} and moisture measurement.¹⁴ The usefulness of the technique is greatly enhanced by the use of sophisticated chemometric statistical analysis,¹⁵ including principal component analysis,¹⁶ partial least squares¹⁷ and fuzzy C-means clustering¹⁸ among others.

However, the current state of the art to determine the dosage and rate of release of the active ingredients in drug delivery devices is through dissolution

measurements. The technique provides a simulation of the expected performance of the system *in vivo* and is an essential QA/QC procedure. However, the procedure is lengthy, especially when the solid dosage form is formulated to provide drug release over many hours. Dissolution studies, however, provide no insight into manufacturing defects when anomalous results are obtained. An independent direct assessment of tablet structure can provide this essential and non-destructive understanding of complex manufacturing failures.

Instrumentation

In recent years there has been tremendous interest and significant developments in infrared spectral imaging using focal-plane array detection. This technique fully integrates infrared spectroscopy and digital imaging techniques.¹⁹⁻²¹ Three technologies have converged to allow the development of these systems particularly for practical applications of high-speed NIR spectral imaging:

- High-performance, uncooled NIR sensitive focal plane array detectors
- Digitally-tunable infrared optical filters
- Enormous increases in PC speed and capacity of laboratory computing platforms

Spectral Dimensions offers complete NIR imaging systems based upon the integration of these components. With these instruments, the spatial relationship and chemical composition of complex matrices, such as pharmaceutical blends, can be rapidly determined. The variation of spectra across the image provides information about the chemical composition as well as the spatial distribution of the components comprising the imaged sample. This novel technique is anticipated to meet the changing analytical needs of the pharmaceutical industry.

The block diagram shown in Figure 2 indicates the layout of the main components of the system. NIR light from the illumination system is focused upon the sample and the diffuse reflectance image of the sample is collected by a microscope objective. Other optical configurations can be used for different sample types and sizes. In practice, data collection proceeds by recording a series of images on the infrared FPA at each wavelength position selected by the tunable filter element. The wavelength range of the experiment and the spectral interval can be pre-determined before data collection begins. All aspects of data acquisition are under computer control with parameters set via a Windows™-based operator interface.

The result is a three-dimensional data set, known as a spectral hypercube, shown in Figure 3. The X and Y axes represent spatial information and the Z axis represents reflectance at the selected NIR wavelengths. Data is analysed using ISys™ (Spectral Dimensions Inc.), a graphical user interface (GUI), and an integrated software package designed specifically for the acquisition, visualisation and analysis of hyperspectral image cubes and maps. NIR spectra associated with any pixel and images associated with any NIR wavelength are readily displayed. The package contains standard spectral analysis and image analysis tools, as well as advanced chemometric qualitative and quantitative analysis capabilities. Based on the Matlab™ (MathWorks, Inc.) programming language, variables used by ISys™ are accessible in real-time by Matlab™, allowing for a large degree of customisation by the expert user. Data is written and/or read in a proprietary file format, and may also be seamlessly read from and/or converted for use by other software packages.

Results

The MatrixNIR™ system was used to examine the internal structure of a “Contac®” time-release granule. The granule was bisected and the diffuse reflectance from the cut surface imaged onto the focal plane array through a 10x microscope objective. Each pixel in the detector array (320 × 240) corresponds to an approximately 6 μm² area of the sample surface. For this particular data set images were obtained at 10 nm intervals from 1000 to 1700 nm, with a total acquisition time of approximately 2 min.

The chemical image shown in Figure 4(b) represents an area of approximately 0.9 mm². This image was generated from the data using principal component analysis and is obtained in a com-

NIR Imaging

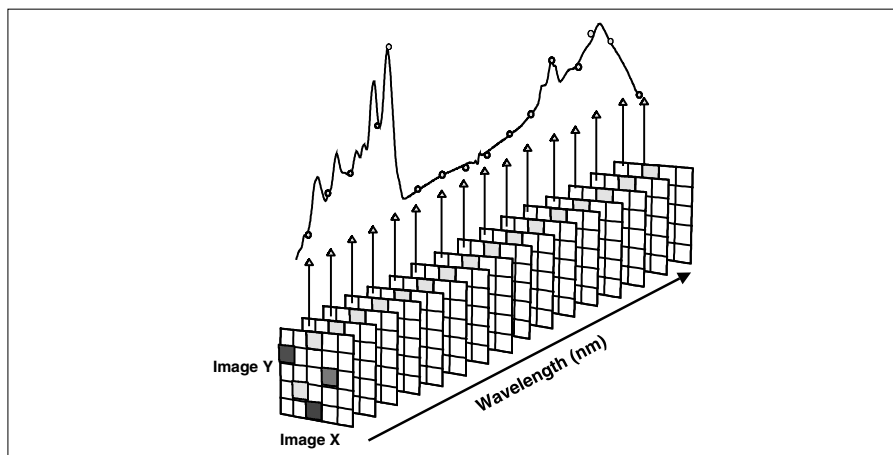


Figure 3. Diagrammatic view of spectral hypercube.

pletely unsupervised manner. Using principal component analysis on a data set such as this is an excellent way to “mine” both spatial and chemical variance within the sample. The analysis produces a series of loading vectors and corresponding scores for each pixel on the array. Examination of the contrast in the score images provides insight into regions of chemical similarity and chemical heterogeneity within the sample. In the example shown [Figure 4(b)], several distinct layers and boundaries are clearly evident in the NIR chemical image and these boundaries are consistent with the known physical structure and composition of this particular formulation. By contrast, the corresponding visible image [Figure 4(a)] reveals no contrast between the respective chemical species and layers. In addition, the NIR spectra associated with each pixel can be displayed by clicking the mouse pointer on any selected region. A single pixel NIR spectrum associated with the central region of the image from 4(b) is shown in Figure 5 and displays excellent signal-to-noise characteristics. This particular data set contains 76,800 equivalent spectra at each spatial location.

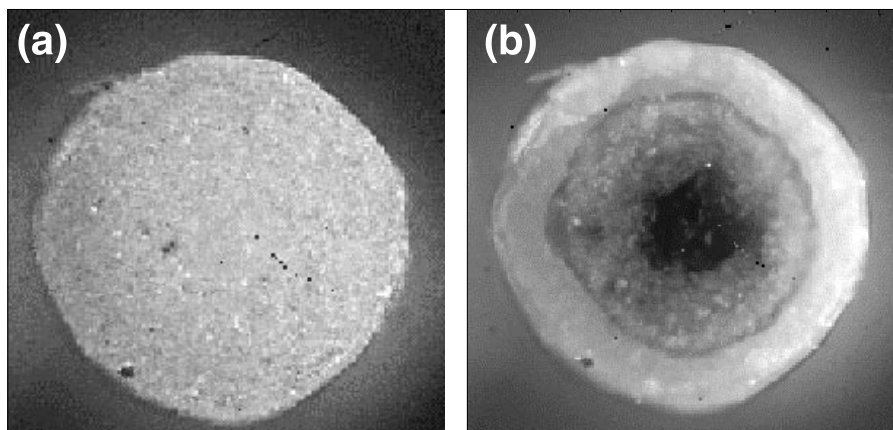


Figure 4. Visible (a) and NIR principal component (b) images of a pharmaceutical time-release granule.

Conclusions

NIR imaging is an exciting new technology capable of providing insight into the structure and function of modern solid dosage forms. It is likely that it will be widely adopted and deployed in pharmaceutical analysis in the future and is particularly applicable to new product formulations and for understanding manufacturing defects.

References

1. S.V. Hammond, *European Pharmaceutical Review* **3(4)**, 47 (1998).
2. F.C. Clarke, R.D. Jee, A.C. Moffat and S.V. Hammond, *J. Pharm. Pharmacol.* **52**, 66 (2000).
3. W.F. McClure, *Anal. Chem.* **66**, 43A (1994).
4. E.W. Ciurczak, *Handbook of Near Infrared Analysis*, Ed by D.A. Burns and E.W. Ciurczak. Marcel Dekker, New York, Ch. 20, p. 549 (1992).
5. M. Blanco, J. Coello, H. Iturriaga, S. Maspocho and C de la Pezuela, *Analyst* **123**, 135R (1998).

6. R. Gimet and A.T. Luong, *J. Pharm. Biomed. Anal.* **5**, 205 (1987).
7. T. Norris, P.K. Aldridge and S.S. Sekulic, *Analyst* **122**, 549 (1997).
8. P. Corti, G. Ceramelli, E. Dreassi and S. Matti, *Analyst* **124**, 755 (1999).
9. A.D. Trafford, R.D. Jee, A.C. Moffat and P. Graham, *Analyst* **124**, 163 (1999).
10. S. Sekulic, H.W. Ward, D.R. Brannegan, E.D. Stanley, C.L. Evans, S.T. Sciavolino, P.A. Hailey and P.K. Aldridge, *Anal. Chem.* **68**, 509 (1996).
11. P.A. Hailey, P. Doherty, P. Tapsell, T. Oliver and P.K. Aldridge, *J. Pharm. Biomed. Anal.* **14**, 551 (1996).
12. E.W. Ciurczak, R.P. Torlini and M.P. Demkowicz, *Spectroscopy* **1(7)**, 36 (1986).
13. A.J. O’Neil, R.D. Jee and A.C. Moffat, *Analyst* **124**, 33 (1999).
14. F.W. Langkilde and A. Svantesson, *J. Pharm. Biomed. Anal.* **13**, 1273 (1995).
15. H. Mark, *Anal. Chem. Acta* **223**, 75 (1989).
16. S. Baronti, A. Casini, F. Lotte and S. Porcinai, *Chemometr. Intell. Lab. Syst.* **39(1)**, 103 (1997).
17. W. van der Broek, E.P.P.A. Derks, E.W. van de Ven, D. Wienke, P. Geladi and L.M.C. Buydens, *Chemometr. Intell. Lab. Syst.* **35(2)**, 187 (1996).
18. J.R. Mansfield, M.G. Sowa, G.B. Scarth, G.B. Somorjai and H.H. Mantsch, *Anal. Chem.* **69(16)**, 3370 (1997).
19. P.J. Treado, I.W. Levin and E.N. Lewis, *Appl. Spectrosc.* **48(5)**, 607 (1994).
20. E.N. Lewis, P.J. Treado, R.C. Reeder, G.M. Story, A.E. Dowrey, C. Marcott and I.W. Levin, *Anal. Chem.* **67(19)**, 3377 (1995).
21. P. Colarusso, L.H. Kidder, I.W. Levin, J.C. Fraser, J.F. Arens and E.N. Lewis, *Appl. Spectrosc.* **52(3)**, 106A (1998).

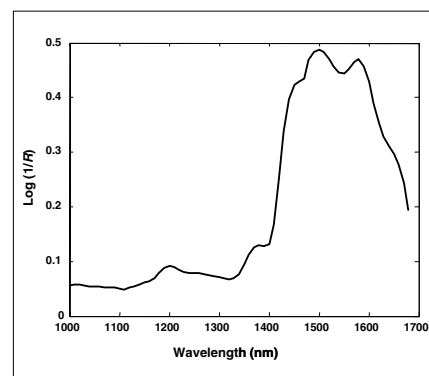


Figure 5. NIR spectrum obtained from a single pixel (6 x 6 μm) in the centre of the image in Figure 4(b).