

Characterization of Solid Dosage Pharmaceuticals by NIR Imaging using the MatrixNIR

Introduction

Solid dosage forms are the most commonly prescribed pharmaceutical formulations. They consist of a mixture of ingredients, combined to provide the desired characteristics. Often, the formulator designs an internal structure to the finished delivery device to facilitate the programmed release of the active components.

It is critical that the formulation be robust and consistent: for every product; any tablet/capsule produced anywhere in the world must have the same characteristics. A basic problem is that formulations with identical ingredients can have radically different performance depending upon how the ingredients are blended together. Drugs are not evenly dispersed within a tablet. Upon micro-examination, the active ingredients are seen in discrete particles or clumps, especially as dosage concentration drops.

Drug dosage management – mixing different drugs in a single dose, extending the period of drug release or providing longer, flatter bloodstream concentration profiles – makes for better performance.

These approaches require sophisticated oral release forms and the need has given rise to a whole new engineering genre. Some of the latest solid dosage delivery forms include OROS tablets, mixed micro-spheres, barrier-layer capsules, cored tablets, inhalable aerosols, barrier-layer transdermal patches and “piggyback” lipid delivery systems.

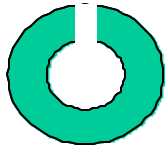


MatrixNIR imaging system

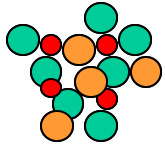
...the most significant factor in determining the quality of a formulated product, is the structure of the matrix that evolves during the manufacturing process... when it is time to assess the quality of our products, we invariably destroy the matrix by dissolving the sample in a solvent. All the information on the physical state of the ingredients and how they relate to each other is then effectively lost...

Steven Hammond, Pfizer

[European Pharma. Rev. 3, 47, 1998.]



OROS, an Alza-developed tablet used by Pfizer and others. It retains its shape in gastric fluids and releases therapeutic doses through an osmotic aperture.



SELECTIVE-RELEASE MICROSPHERES, drugs with selected target therapies are adsorbed onto inorganic or polymeric microspheres. Concentrations and release rates are staggered to provide a complex therapeutic pattern in the bloodstream.



BARRIER-LAYER RESERVOIR CAPSULE, As the drug releases, additional drug refreshes the concentration in the upper chamber to maintain constant concentration. This dosage form provides long plateaus of drug in the bloodstream.



CORED TABLET, used for sequential delivery of one drug at two distinct concentrations or back-to-back dual drug delivery.

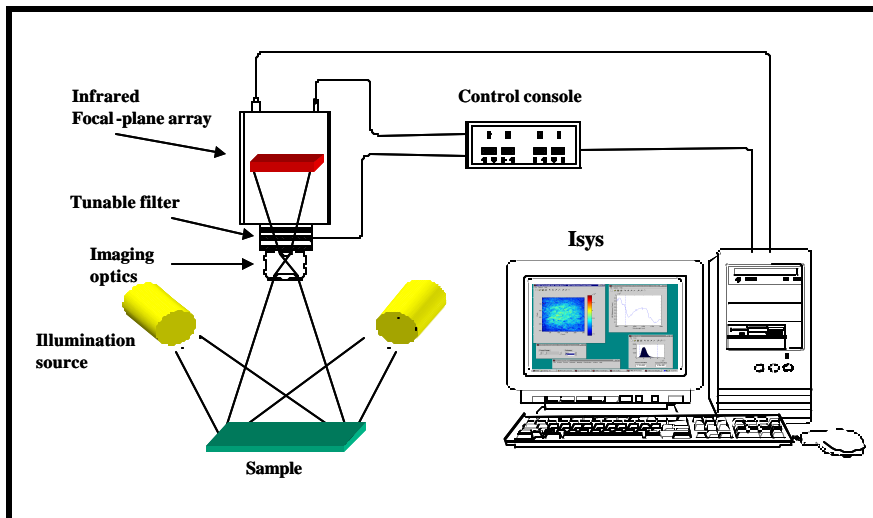
NIR (near Infrared) Imaging

NIR (near-infrared) spectroscopy is widely accepted within the pharmaceutical industry as a tool for bulk materials characterization.

In the NIR wavelength region (0.9 - 2.5 μ m), the overtone and combination bands of the C-H, O-H, and N-H stretching vibrational modes provide highly specific molecular information for species identification.

Attempts have been made to use infrared micro-spectroscopy to locate the components within a dosage form matrix by “mapping” the sample using an XY stage. The spatial resolution is poor and the time taken is great.

However, it is now possible to combine NIR spectroscopic information with direct imaging of the spatial distribution of the components that make up the dosage form matrix. For the first time, direct observation of the chemical structure of the dosage form can be realized in near “real-time”.



Diffuse reflected NIR radiation from the surface of the sample is collected by a series of imaging optics and passes through a NIR tunable filter before forming an image on an infrared focal plane array detector.

The filter is continuously stepped through a predetermined spectral interval and an image at each wavelength is stored. The resulting data hypercube is analyzed by ISys, a proprietary PC-based software package.

Block diagram of the major components of the MatrixNIR system

Time Release Granules

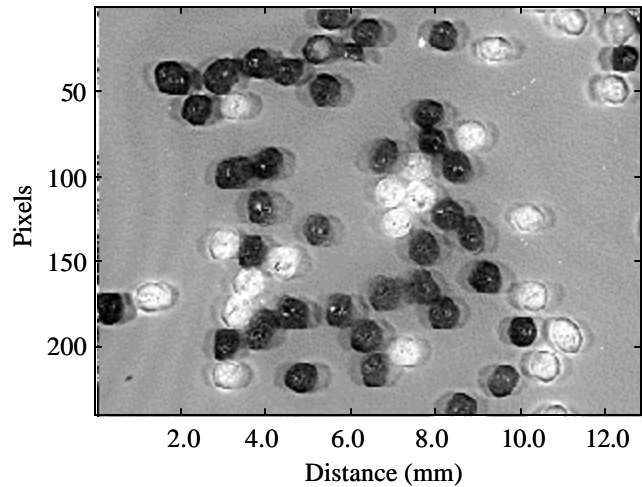
Encapsulation of the active ingredient into micro-spherical granules allows sustained release over extended time periods. Granules of differing solubility are packaged together into a single capsule that staggers the release of the active ingredient in a complex pattern.

The distribution of different granules within a capsule may be determined by spreading the granules out and imaging the separated particles. By choosing the appropriate wavelength, different granules are chemically differentiated. This makes use of the MatrixNIR's ability to image a relatively large area (9x12 mm) in macro mode and conduct massively parallel spectroscopic measurements.

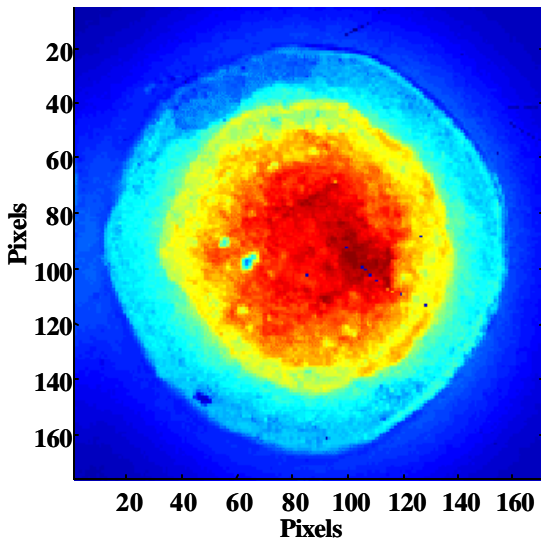
On closer examination, using the system's micro mode, each granule can be seen to have an internal structure that determines its active release characteristics.



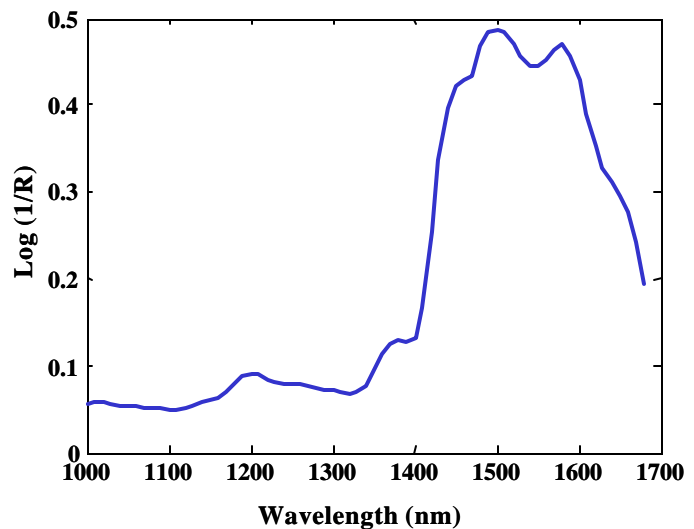
A typical, cold medicine, time release capsule



The image obtained, at 1520nm, from a selection of time release granules within a single capsule.



The image above shows the chemical structure of a single, time-release granule (less than 1 mm in diameter) from the same cold medicine capsule shown at above right. The NIR reflectance spectrum at right represents the molecular fingerprint behind a single pixel from the central region of the granule.



Active distribution in tablet forms

Acetaminophen, is the active ingredient in Tylenol, a common analgesic. An Extra-Strength Tylenol tablet contains 500 mg of acetaminophen, approx. 85% of the total tablet weight.

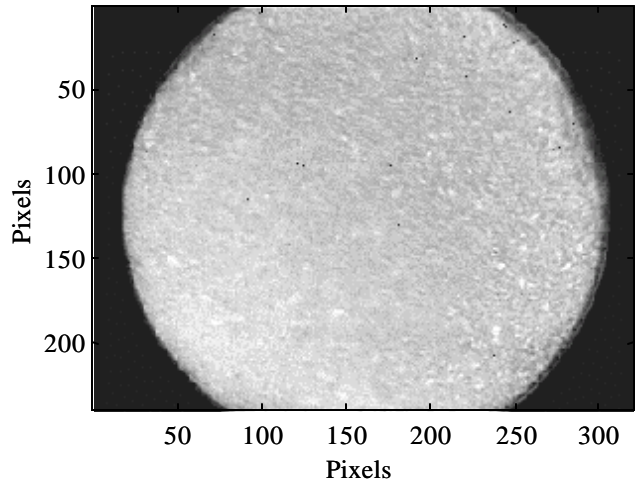
Each tablet is approx. 15 mm in diameter and virtually the whole tablet may be imaged in macro mode.

NIR spectra were then collected at 10nm intervals from 950 - 1170 nm and the data cube subjected to Principal Component Analysis. The entire data set may be collected in less than 1 min. One PC image is shown at right and confirms the even distribution of the active ingredient throughout the tablet.

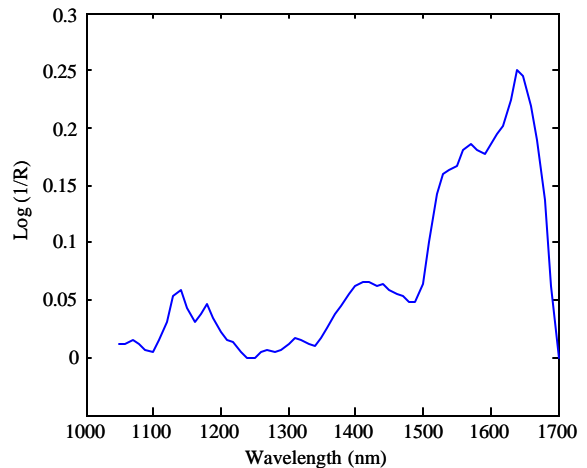
The reflectance spectrum from a single pixel in the image compares favorably with pure acetaminophen.

Children's Tylenol contains only 80 mg of acetaminophen, approx. 20% of the total tablet weight. Feeding the acetaminophen spectrum into the Children's Tylenol image cube (a reverse spectral search) produces the PC image below right, which shows the active component distribution.

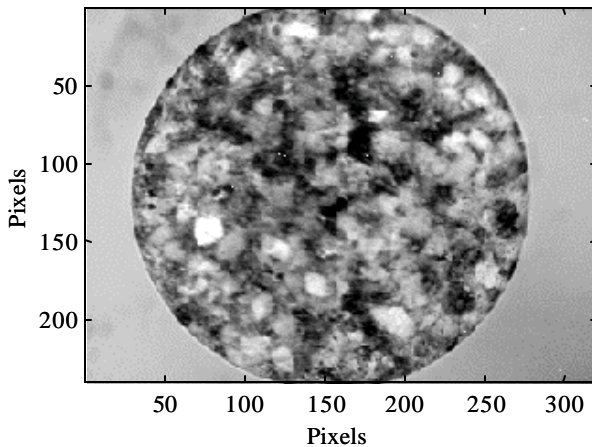
Another major ingredient of a Children's Tylenol tablet is a combination of sugars. Selecting for the sugar absorbance produces the complementary distribution below.



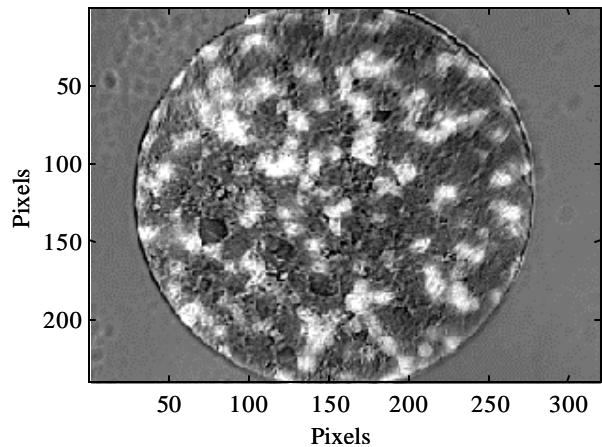
PC Image of Extra-strength Tylenol tablet



Single pixel NIR spectrum of acetaminophen



Distribution of "sugar" components in Children's Tylenol



Distribution of active ingredient in Children's Tylenol (containing approx. 20% acetaminophen)