

Near Infrared Chemical Imaging

A powerful tool in the QbD armory

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Quality by Design (QbD) is a key part of the revised regulatory approach currently transforming the pharmaceutical industry. QbD demands greater understanding of the product during formulation and process development stages, but delivers significant rewards - improved process efficiency, greater flexibility and a lighter regulatory touch. Its adoption, coupled with implementation of the PAT initiative, is promoting a shift from empirical development and control to knowledge-based manufacture.

Accessing information that gives insight into critical aspects of performance is essential when designing quality products and robust manufacturing processes. Near infrared chemical imaging (NIR-CI) is one very powerful analytical technique that rapidly delivers highly relevant data. NIR-CI is a real 'go to' choice for the pharmaceutical industry that can be used in a variety of ways to improve product understanding.

Quality by Design

One of the steps needed to obtain regulatory approval for a new product is to define the manufacturing process. Conventionally the process has been specified down to the level of a single operating point, including values for variables such as the speed of rotation of the mill, blending time, or drying temperature. These values often are not defined on the basis of a goal - for example, the specification may be to "blend at 15 RPM for 15 minutes" rather than "blend until the components are well mixed". Once established through the validation process, defined operating parameters cannot be changed without reference to the regulatory authority, discouraging ongoing process development. A similar approach applies when specifying product quality; the variables involved in the definition of what constitutes acceptable product are not always directly related to product performance.

QbD challenges the industry to identify those variables which actually have an impact on critical aspects of product performance, and then to design a process that effectively controls them. The emphasis is to identify an operating window within which a product with the required performance characteristics is produced consistently. Instead of defining the manufacturing process in terms of every possible variable, the move is to define it only in terms of those that are important.

This approach requires much greater process and product understanding than has traditionally been developed. It is no longer sufficient to simply set a variable at a value of x : now the developer must understand the impact of varying x within a defined range, and the effect on x of other variables, such as change in raw material or equipment. This information is used to specify the design space. One of the benefits of QbD is that changes within the design space are easy to implement, giving operational flexibility. Consequently, effectively defining the design space is now a critical part of process development.

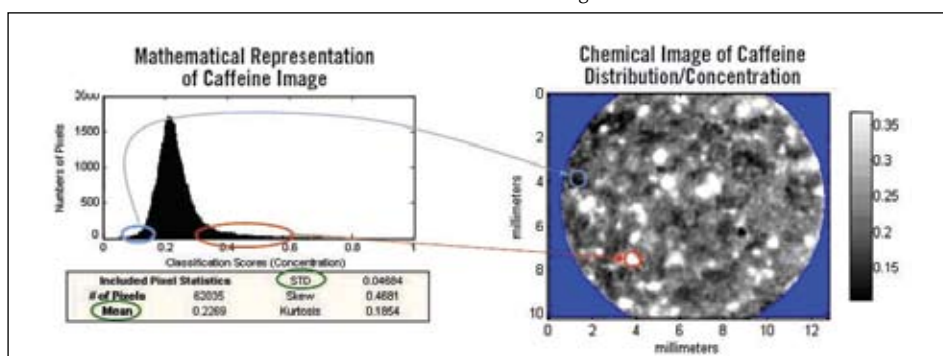


Figure 1: NIR-CI applied to caffeine-containing tablet

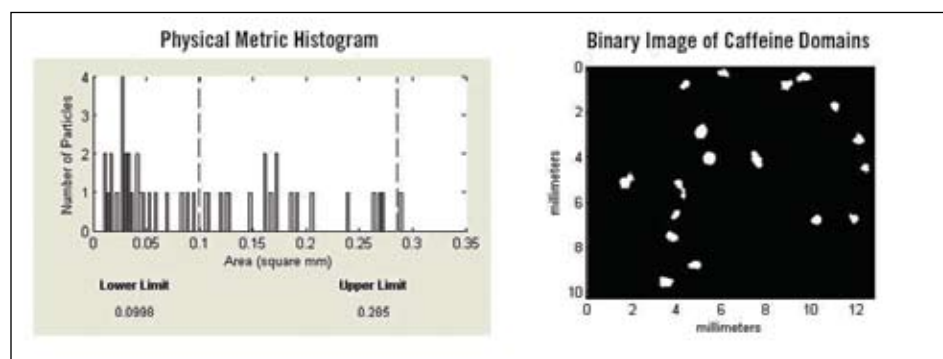


Figure 2: Caffeine concentration

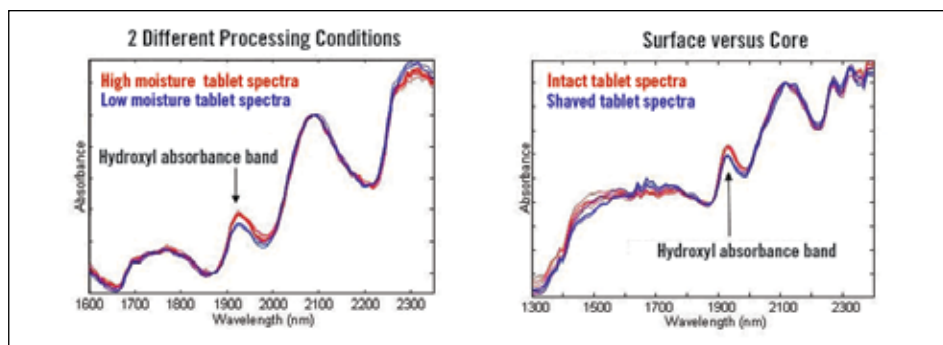


Figure 3: The effect of different processing conditions

NIR-CI

NIR-CI, as the name suggests, combines the species de-

NIR-CI And QbD

tection capabilities of near infrared spectroscopy with the spatial resolution provided by imaging techniques. A near infrared chemical imaging system collects tens of thousands of NIR spectra in about a minute. It provides data that can be used to determine where a chemical species is located, as well as what it is and how much is present. NIR-CI is therefore ideal for studying not only the composition, but also the heterogeneity, structure and nature of components in a product. As an example, it is one of the few tools that can be used to examine co-localization (or aggregation) of sample components, a factor known to affect product performance.

Equally important are the practical attractions of NIR-CI, which include:

- Rapid analysis, particularly when only a few wavelengths are of interest
- No sample preparation
- Suitability for a wide range of materials – powders, granules, tablets (round and flat faced), highly colored samples
- Rugged and easily automatable instrumentation
- Variety of magnifications to optimize the area of analysis

These factors make NIR-CI ideal for studying the structural elements of a sample and/or differences between formulations that may account for variations in performance. An entire tablet can be analyzed rapidly. If warranted, further analysis, at higher magnification, can provide more detailed information to refine understanding.

How It Works

NIR-CI detects the presence of different chemical bonds, particularly O-H, N-H and C-H, by measuring optical absorption in the 1200-2450 nm range. Quartz halogen lamps provide an easily configurable source of illumination. Images are captured using a two-dimensional array. The array, a distinguishing feature of true NIR-CI analyzers, eliminates the need to move the sample relative to the detector, accelerating measurement and simplifying instrument design.

Modern NIR-CI systems can be configured to study either a small sample - a single granule, for example, or a larger region, perhaps a complete blister pack. If complete spectra are required measurement is complete in just over a minute, but if only a few wavelengths are of interest then this time is reduced to seconds. This flexibility makes NIR-CI suitable for high throughput QA/QC applications as well as in-depth laboratory analysis.

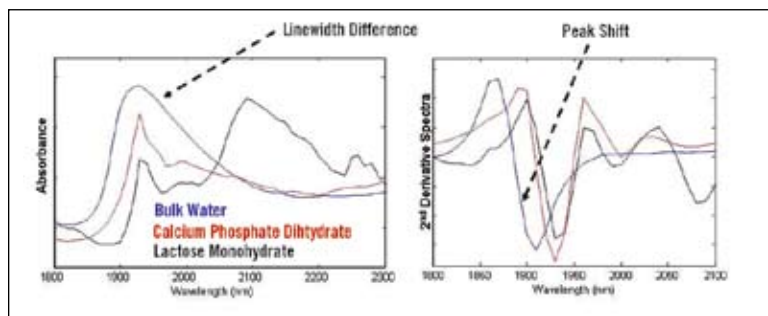


Figure 4: Bulk versus bound water

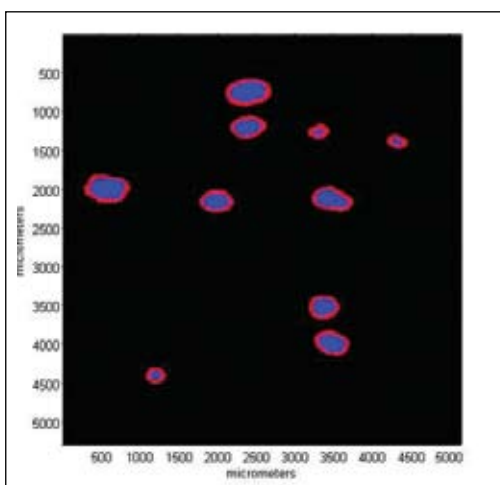


Figure 5: Coated granules in cross-section

Analyzing NIR-CI data

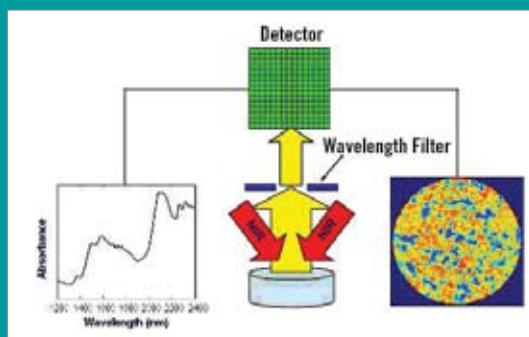
One question that arises with NIR-CI is how to summarize the tremendous amount of information contained within a chemical imaging data set. Tens of thousands of spectra are gath-

ered during a single measurement making effective data analysis essential. Malvern provides ISys, a chemical imaging data analysis package in which the mathematical methods used are advanced, but widely accessible in the form of user-

friendly graphical user interfaces. Statistical and quantitative tools allow the easy extraction of both chemical and morphological information providing an objective summary of key image parameters, such as heterogeneity, as described in the following example.

Figure 1 shows an image of a tablet containing caffeine. Each pixel has been colored to reflect concentration, brighter areas being associated with higher levels of caffeine. At this magnification each pixel is 40 X 40 microns in size. The histogram associated with the image represents this data quantitatively, pixels in the sample with a given concentration being grouped for display purposes. The power of this representation is that the analyst can use histogram values to provide an objective characterization of the sample. For example, the mean of this distribution is proportional to the overall concentration of caffeine in the tablet, comparable to values provided through HPLC and single point NIR spectroscopy. The additional information provided though, is the distribution of values across the sample. Characterizing this distribution, for example by examining the standard deviation of the histogram, provides information on the heterogeneity of a sample. A narrower distribution indicates greater sample homogeneity i.e. all the pixels have similar concentrations. By comparing mean and standard deviation values, samples can be objectively ranked by heterogeneity without the need for the analyst to make judgements based on subjective image interpretation.

It is also possible to categorize the size, morphological properties, and distribution of chemically distinct domains; this is a powerful analytical technique for samples with heterogeneous domains. A binary image is generated to highlight the domains of high caffeine concentration (see figure 2). The threshold above which a pixel is classified as caffeine (white) may be determined using objective statistical methods, to ensure reproducibility. Pixels that



Principal components of a NIR-CI instrument

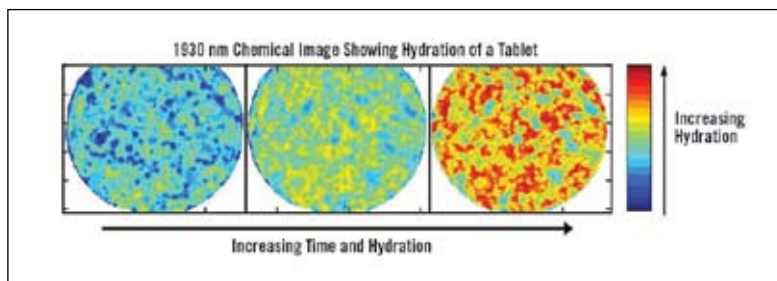


Figure 6: Chemical image showing hydration of a tablet

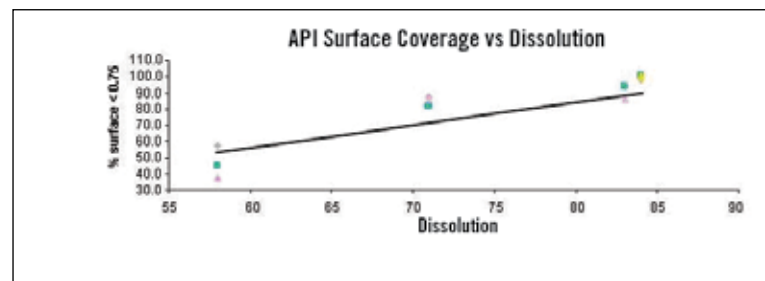


Figure 7: The relationship between API surface coverage and dissolution

do not meet this level are classified as something else (black). Using these results the morphological attributes of the caffeine-rich areas can be investigated, for each domain, or for the tablet as a whole. Classification can be on the basis of any size or shape parameter. For some applications the size and area coverage of the domains may be important while in others distribution statistics, which quantify heterogeneity, may be significant.

The following examples show how this type of analysis can be used to study practical problems relating to QbD implementation. In each case NIR-CI provides a fast and efficient solution.

Assessing the impact of processing conditions on moisture content

Hydroxyl groups are strong NIR absorbers, creating a characteristic band at around 1930 nm that can be used to detect water in a sample. Figure 3 shows spectra for tablets manufactured under different processing conditions.

The two samples are ostensibly the same but have noticeably different moisture content. Comparing images of the surface of a tablet with those of the interior (a shaved tablet) reveals the location of this water. Moisture is held predominantly in the outer layers of the tablet rather than the core. Both findings promote process understanding and, as the localization of water can impact the dissolution properties of a sample, provide valuable insights into product performance.

Investigating the nature of material in a sample

With NIR-CI it is even possible to distinguish water that is bound to other sample components (forming hydrates) from water simply present within the sample (bulk water), as hydrogen bonding differences between these two types of water produce a variance in the NIR spectrum.

Figure 4 shows that bulk water produces a

broad peak that clearly differentiates it from bound water present in the form of hydrated salts. Second derivative spectra exhibit a peak shift which is even easier to detect than the difference in line width. The form of water in a sample can be studied easily using this technique.

Investigating the homogeneity/heterogeneity of granules

Ideally, uncoated granules are homogeneous in both morphology and composition. Coated granules are often designed to have a homogeneous core surrounded by a uniform coating. In practice, however, an active pharmaceutical ingredient (API) may be distributed unevenly, either across a sample or within each individual granule. Size and shape may also vary, impacting product performance. With NIR-CI, granules can be investigated individually or as a complete dose. Imaging individual granules in cross-section may be beneficial particularly for coated materials.

Figure 5 shows images of coated granules in which the core and coating material are sharply contrasted. The thickness of the coating is easily measured. Analysis of the associated data allows the investigation of coating thickness both for individual granules and for the sample as a whole. Coating uniformity can therefore be quantitatively assessed.

Understanding hydration behavior

The spatial resolution provided by NIR-CI literally adds an extra dimension to hydration studies. Figure 6 shows images of a tablet held in a humidity chamber for an increasing length of time.

Moisture content is clearly rising as the experiment progresses – an expected trend that could be adequately tracked using single point NIR. The additional information that NIR-CI provides is that water is not distributed uniformly within the sample. In this case the water

is binding to an excipient, clustering in areas of high excipient concentration. Water gradients or heterogeneous water distribution within a sample are both readily highlighted using this approach.

Exploring the link between species distribution and product performance

When there is a direct correlation between the spatial location of a species and product performance NIR-CI is particularly useful. Figure 7 shows a direct correlation between API surface coverage and dissolution rate for a specific sample. Dissolution rate is a key performance parameter for many pharmaceuticals, directly influencing uptake in the body.

API surface coverage can be measured directly by appropriately processing spectral data. API is differentiated from the rest of the granule to highlight API-rich domains which are then sized to yield a value for overall surface coverage. Because the technique is non-destructive, the same samples that have been analyzed using NIR-CI may subsequently be subjected to dissolution testing. NIR-CI coupled with dissolution testing therefore allows rapid assessment of the effect of API surface coverage on dissolution time.

Conclusion

The successful implementation of QbD demands greater understanding at the formulation and development stages of pharmaceutical processes. Analytical tools that provide relevant information are therefore extremely valuable. NIR-CI is a powerful, flexible technique that rapidly delivers critical data. Suitable for granules, powders and tablets of all shapes it is excellent for studying homogeneity/heterogeneity, the nature of species in a formulation and morphology. Correlating these data with performance characteristics develops the understanding and knowledge that underpin QbD. ■