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New methods for determining uniformity of formulations

Chemical sciences

The uniformity of a drug product's contents is a parameter that requires constant monitoring. It is important from a handling/processing standpoint, and it is of the utmost importance for patient safety to ensure that the correct dose is delivered every time.

Characterising content uniformity is a laborious process typically performed by two methods:

- Content uniformity – performing concentration measurements on 30 units of product
- Weight variation – weighing 30 units of product and assessing variation

Both methods are well established but there are problems with each.

Content uniformity:

- Is time consuming – requiring serial dilutions, calibration and quantification of each constituent
- Destructive – requiring samples to be dissolved so they can be assayed
- Has limited qualitative information – will only give concentration measurements and no detail about how well dispersed the constituents are within a single sample

Weight variation:

- Provides no information about the contents or concentration of constituents within a tablet
- Provides no information about the distribution of constituents within a tablet

Both these methods are limited in their ability to help understand critical quality attributes and how these are affected by processing parameters and material attributes. Renishaw's RA802 Pharmaceutical Analyser offers a new way of determining uniformity, giving more comprehensive information than both techniques, whilst also being considerably faster than the two current methods.

Centre of Area (CoA)

The RA802 Pharmaceutical Analyser collects Raman spectra from across the sample surface. These are then processed to identify the constituents and generate chemical images that show the domains of individual formulation constituents.

To quantify the uniformity of constituents within tablets we use a metric which we call centre of area (CoA).

The software takes the chemical image and determines the location of the centre of area of a given constituent. The CoA is the distance to this location from the centroid of the tablet, normalised by half the tablet's largest dimension in the image. A CoA of zero indicates that the constituent is not biased to one side of the tablet or another. A CoA of 100% would show that the constituent is solely in one compact particle at the edge of the tablet.

CoA is just one of the many parameters that can be generated from the chemical images, but it does give a good overview of tablet uniformity; any value appreciably different from zero indicates that the constituent is not uniformly distributed.

Poor uniformity of constituents within single tablets will inevitably lead to inter-tablet variation. The RA802 can analyse inter and intra-tablet uniformity.

Renishaw RA802 Pharmaceutical Analyser

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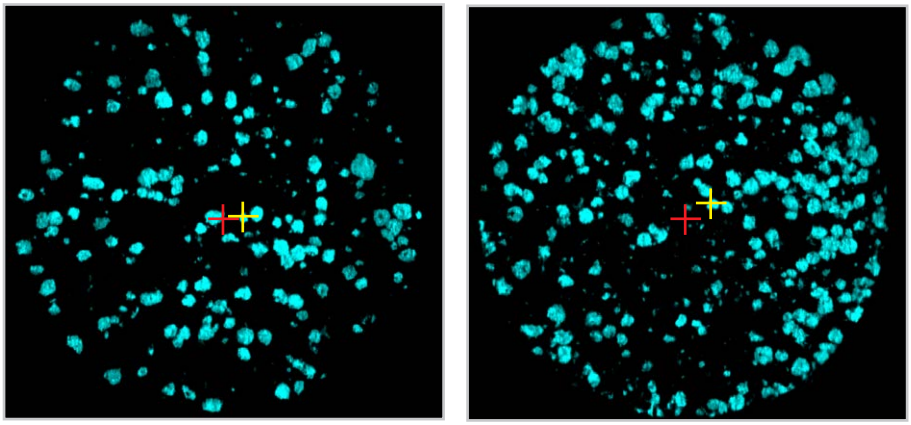
Case study – Uniformity of API distribution in in-spec and out-of-spec batches



Raman image of API distributed in tablet of in-spec batch (left) and out-of-spec batch (right). The centre of the sample is indicated by the red cross, and the CoA is indicated by the yellow cross.

Above are examples of two tablets containing the same API, one from an in-spec batch (left) and the other from an out-of-spec batch (right). Both batches passed the conventional content uniformity tests, however, both performed very differently during their dissolution tests.

Tablets in the out-of-spec batch dissolved more quickly than those of the in-spec batch, however, the content uniformity data suggested that the batches were identical.When analysed using the RA802 Pharmaceutical Analyser it became evident that the API within the tablets was distributed very differently between the two batches.

The in-spec batch consisted of larger particles which were more uniformly distributed throughout the tablet.

The out-of-spec batches tended to have a larger number of smaller particles and the distribution was less uniform. For example, the loading of API in this out-of-spec tablet appears to be biased to the right.

Having the images is useful as it allows users to clearly visualise the difference between the two batches. However, the real power of the system is in its ability to generate numbers from these images which can be used to compare against past and future batches enabling decisions to be made and problems to be identified quickly.

	Particle Statistics	
	In-spec batch	Out-of-spec batch
Equivalent circle diameter (d50)	191 µm	175 µm
CoA (lower % is more uniform)	2.3 %	9.6 %

Conclusion

The conventional methods for determining content uniformity will remain for the foreseeable future. However, these offer the user limited scope for truly understanding the uniformity within and between samples and may not be able to provide all the information required when trying to diagnose batch variation problems.

At Renishaw we have seen numerous examples where content uniformity could not be characterised sufficiently by conventional methods. The RA802 Pharmaceutical Analyser's CoA function can be used alongside standard experimental techniques for content uniformity determination, but it can provide more comprehensive information on the nature of the formulation and why one batch performs differently to another.

Renishaw. The Raman innovators

Renishaw manufactures a wide range of high performance optical spectroscopy products, including confocal Raman microscopes with high speed chemical imaging technology, dedicated Raman analysers, interfaces for scanning electron and atomic force microscopes, solid state lasers for spectroscopy and state-of-the-art cooled CCD detectors.

Offering the highest levels of performance, sensitivity and reliability across a diverse range of fields and applications, the instruments are designed to meet your needs, so you can tackle even the most challenging analytical problems with confidence.

A worldwide network of subsidiary companies and distributors provides exceptional service and support for its customers.

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