In the Mix

When manufacturing safe and effective drugs, it is essential that the amount of active pharmaceutical ingredient present in every dose is exactly the same. During production of solid oral dosage forms, the key challenge is to obtain a homogeneous blend before tableting or filling, in order to achieve the required content uniformity of the final product

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Achieving an acceptable level of blend uniformity (BU) during pharmaceutical manufacture is a necessary prerequisite for delivering content uniformity; inhomogeneity and a skewed active pharmaceutical ingredient (API) to excipient ratio could affect drug bioavailability and efficacy, potentially inducing an adverse response in patients.

However, achieving BU can be difficult, especially when the ratio between the API(s) and excipients is high. For example, a cough and cold remedy may contain 5mg of phenylephrine in a 3,200mg effervescent tablet – a ratio of 1:640. Ensuring an equal distribution of API molecules under such conditions often requires specific blending processes and ongoing process monitoring to ensure BU remains at the desired level.

Commonly, all ingredients are blended in free-fall or high-shear mixers with pre-set rotation speeds and blending times. Blending parameters are often based more on experience than on analytical data. With Quality by Design (QbD) now being frequently required by regulatory bodies to ensure that pharmaceutical products are of the quality necessary for patient use, blending specifications would ideally be based on a data-driven approach (1).

Fortunately, as process analytical technology (PAT) tools optimised for this purpose become more readily available, these requirements can be fulfilled in an easier and simpler manner than with many traditional off-line approaches (2-4). Implementation of PAT means that qualities pertaining to both manufacturing equipment (critical process parameters) and the product (critical quality attributes) are carefully controlled and defined based on scientific data. This allows manufacturers to generate products of a consistent quality, contributing to a potential reduction in both out-of-specification batches and overall costs. PAT tools – such as multivariate data analysis (MVDA), modern spectroscopic instruments (for real-time measurements) and continuous improvement – allow for faster, more informed decision-making during the manufacturing process.

Quality by Design

QbD represents a paradigm shift away from an experience-based approach to a systematic, risk-based one. To underline the importance of this method, a 2007 report from the FDA emphasised that: "Quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured, along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks" (5).

Furthermore, the FDA's QbD approach was supported by guidance from the ICH; notably, the implementation of directives ICH Q8: *Pharmaceutical Development*, ICH Q9: *Quality Risk Management*, and ICH Q10: *Pharmaceutical Quality System* (6).

As of January 2013, the FDA also requires generic drug manufacturers to implement QbD into their abbreviated new drug applications (ANDA) (7). The FDA and EMA have recently extended a pilot programme of QbD parallel assessment in order to ensure consistent adherence to international guidelines related to QbD – an approach that will promote the consistency of product quality throughout the EU and US (8). Given these directives, it is likely that the industry will soon be employing and insisting upon a QbD approach throughout pharma manufacturing as standard.

Testing Technology

Many of the technologies facilitating the blending process have advanced significantly since their inception. Techniques such as near-infrared (NIR) and Raman spectroscopy are increasingly common and are being paired with chemometric techniques and MVDA to improve the accuracy of data capture and evaluation. These spectroscopic techniques allow for on- and in-line measurements coupled with active process controls (closed-loop control), permitting a very fast and less invasive data acquisition process compared with traditional analytical

methods, as well as being consistent with the FDA's PAT initiative (4).

Blending Procedure

While there are a variety of blending techniques available, two commonly employed approaches involve the use of free-fall and high-shear mixers (see Table 1).

Setting the correct blending time based on empirical investigations is also critical: a blending time that is too short can lead to inhomogeneity, whereas blending times set too long can result in downstream processing issues (such as hampering flowability due to particle size). Incorrect blending times can adversely affect not only the properties of the final product, but also costs.

The current practice of determining the optimal blending parameters (see Table 1) to achieve a uniform blend in these devices consists principally of blending for a predetermined length of time, stopping the device and manually removing a specimen. This specimen is then analysed by traditional methods such as ultraviolet-spectroscopy or high-performance liquid chromatography (HPLC) (9), which are often time-consuming and invasive, while also being a potential source of contamination. Fortunately, NIR spectroscopy is well-positioned to overcome many of these drawbacks.

Table 1: The pros and cons of free-fall versus high-shear blending

Free-fall blending	High-shear blending
Process	
• A container filled with API and excipient is sealed and rotated for a specified length of time and at a set speed (rpm) • Excipients may be added throughout the process to improve blending results • The fill level and rpm can only be adjusted within tight limits • The other main adjustable parameters are blending time and number of blending steps (for example, adding excipients all at once or in separate batches)	• An agitator moves within a bowl filled with API and excipients, much like a kitchen mixer • The rpm can be adjusted within a relatively large range • The fill level can only be adjusted within tight limits • The main adjustable parameter is blending time and rpm • The geometry of the agitator can be adjusted to improve blending results
Pros	
• Enables a slow rotating speed, ensuring uniform, gentle blending • Low impact, so helps prevent unwanted destruction of granules	• PSD and morphology of excipients and API is less critical; agglomerates are resolved; and even poorly flowable materials – including fluids (such as oils) – can be used
Cons	
• Particle size distribution (PSD) and morphology of excipients and API need to be similar to avoid segregation – poorly flowable materials are harder to blend	• Relatively high impact, so can result in granule destruction • Cooling may be required since the process results in temperature elevation (which, in turn, can lead to API degradation)

Qualitative and Quantitative

NIR spectroscopy is an innovative approach to monitoring and controlling BU. It offers a number of benefits, primarily because the analytical technology is in-line and provides spectral data at an instant, avoiding the need to interrupt the process. A mobile NIR spectrometer is directly attached to the blender and linked to a computer. Data is recorded through a sapphire window in the blending container, while a three-dimensional position sensor and software-controlled trigger-switch initiates the capture of spectral data (approximately 10 spectra per rotation). Data are only captured when the product mixture is present at the window. Spectral data are then sent via a wireless local area network to a computer for real-time analysis.

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Case Study: Effervescent Tablet Formulation

The formulation of an effervescent tablet that was examined for this case study involved a two-step blending process. Firstly, the API was mixed with approximately 50% of the excipients. In the second stage, the remaining 50% of the excipients were added and blended with the mixture.

The blending times for these steps had traditionally been based on experience and commonly used settings, rather than verified data based on scientific investigation. The focus of this case study was to perform an examination of the mixing process, and to determine whether or not blending times could be adjusted to reduce production time (and therefore cost) without impacting BU (and, by extension, product quality).

Methods

An NIR spectrometer mounted on the blend container was used to record spectra (see Figure 1). In order to avoid possible interference from the excipient during data analysis, specificity was ensured by recording spectra of both the API alone and the matrix formulation alone (meaning the entire formulation mixture minus the API).

Calibration samples were recorded at a range of API concentrations and also analysed via HPLC. Standard normal variate was utilised for spectra pre-treatment. A quantitative model was employed using partial least squares with the spectral data and HPLC assay results as reference values. Making use of this model, API concentration was predicted for the production data and plotted against the blending time (number of revolutions). A low variability in the predicted assay values is indicative of blend homogeneity.

Results

A good correlation for the calibration plot was achieved (see Figure 2) and the associated production data clearly highlight both blending steps in this case (see Figure 3). The data from the quantitative model show that homogeneity for the first blending step is achieved after approximately 40 revolutions. After adding the second half of the excipients to the mixture, BU is achieved following another 35 revolutions; thereafter, no significant improvement is seen. The predicted concentrations from the second blending step correlate well with the label claim, as confirmed by laboratory quality control analysis of the final product.

The data presented here show that NIR spectroscopy is highly sensitive, to the point that it can even be used to differentiate the direction of container rotation. Based on the analysis of these results, it was determined that the blending time could be shortened by approximately 50 revolutions without affecting product quality.

Figure 1: Production blender with the NIR instrument 'SentroPAT BU' attached

Figure 2: Quantitative calibration model built on calibration samples with API concentrations of 80%, 90%, 95%, 100%, 105%, 110% and 120% of the label claim. Samples were prepared in lab scale and spectra recorded using a lab scale blender

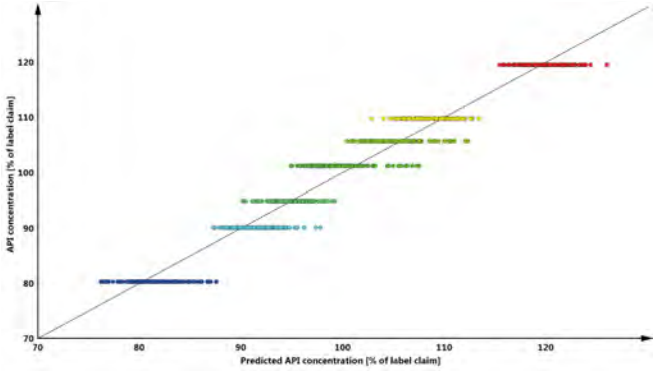

Figure 3: Assay values during the blending process. Blue: blending step 1; green: blending step 2. The periodic fluctuations of the assay values are attributable to the rotating direction of the blender

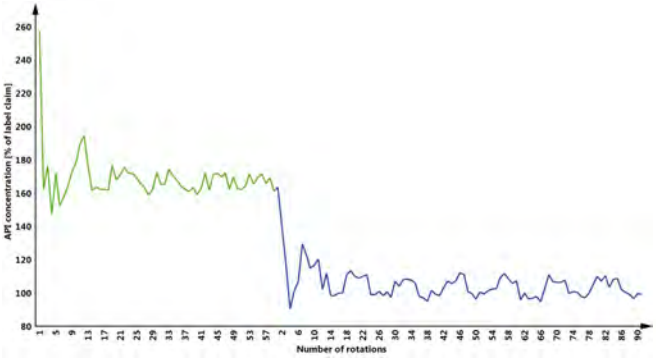

Table 2: Qualitative and quantitative NIR models for determining BU

Qualitative NIR models	Quantitative NIR models
• Principal component analysis performed to reduce multivariate data into a few linearly uncorrelated variables – the principal components (PCs) • In a PC score plot, the data points tend to move towards each other with increasing blending time • The distance between data points represents the variance of the spectra/mixture • This model, if created off-line, can be used for routine production and the data can be included to assess BU and inter-batch variability	• NIR spectra of calibration mixtures with varying concentrations of API are recorded • A specific number of spectra are recorded at each concentration and analysed followed by spectral band deconvolution and identification of characteristic wavelengths of the API • Calibration mixtures are also analysed via a reference method, such as HPLC • NIR spectra from the product blend and reference data are correlated using partial least squares regression to build a calibration model • BU can then be predicted by plotting API concentration against blending times/revolutions

The most common method of assessing BU from these data is by analysing the standard deviation of the spectra, known as a moving block standard deviation test. The BU end-point has been reached once the variation in the spectra readout is consistently below a certain critical limit for a specified period of time. NIR models constructed using this data can be either qualitative or quantitative (see Table 2).

Content Uniformity

From both a quality and regulatory stance, QbD continues to grow in importance and offers substantial potential savings to process costs. As blending is frequently an integral part of creating a high-quality pharmaceutical product, it makes sense to base blending parameters upon evidence rather than experience.

The ever-evolving sophistication of PAT tools and processes specifically developed for this purpose will enable manufacturers to carry this out with greater accuracy, control and reproducibility. By infusing QbD supported by PAT into processes, it is possible to significantly reduce manufacturing times and costs, while ensuring the products created are of a quality and consistency required by regulatory bodies, healthcare practitioners and patients alike.

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Dr Detlev Haack, Director of R&D at Hermes Pharma, earned his PhD at the University of Hamburg on the subject of chemical and physical stability of Piroxicam in solid dispersion with PEG and PVP. In 1997, he received approbation as a pharmacist. From 2003-2007, Detlev was Manager of Sales and Business Development at Hermes Arzneimittel GmbH. He held the position of Associate Director of R&D there from 2007-2012 before becoming Director of R&D in 2013. His career also includes a previous position as Head of Production at Altana Pharma Oranienburg GmbH.
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